What is effective for preventing CKD progression?

Clinical Evidence and Personal Experience in Caring
Diabetes and Non-Diabetic CKD Patients

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健保醫療支出10大疾病 慢性腎病居首

The Central News Agency 中央通訊社
2019年9月2日 下午5:02

（中央社記者陳偉婷台北2日電）

衛福部健保署統計，107年醫療支出前10大疾病，慢性腎病排名第一，年花健保約新台幣513億元，第二名是糖尿病，第三名則是齒齦炎及牙周疾病。

根據衛生福利部中央健康保險署統計資料，107年健保支出最高的10大疾病排行為慢性腎臟疾病，就醫人數約36.4萬人，醫療費用約513億元。其次為糖尿病，就醫人數145.9萬人，費用約291億元；齒齦炎及牙周疾病，就醫人數877.8萬人，約花費171億元。

其他疾病依序為齲齒、高血壓、到院抗腫瘤治療、呼吸衰竭、慢性缺血性心臟病、思覺失調症及急性上呼吸道感染。

案例分享

一位 **56**歲男性，患第二型糖尿病, 高血壓及痛風已**10**多年, 已併發視網膜病變,

職業是大貨車司機, 三餐不定時, 食量大, 每天 **1** 包菸抽 **30**年,

身高 **177 cm, 體重 100.6 kg, BMI 32.9**

HbA1C 9.4 %, BP 184/101 mmhg, LDL-C 148.6, Uric acid 9.5,

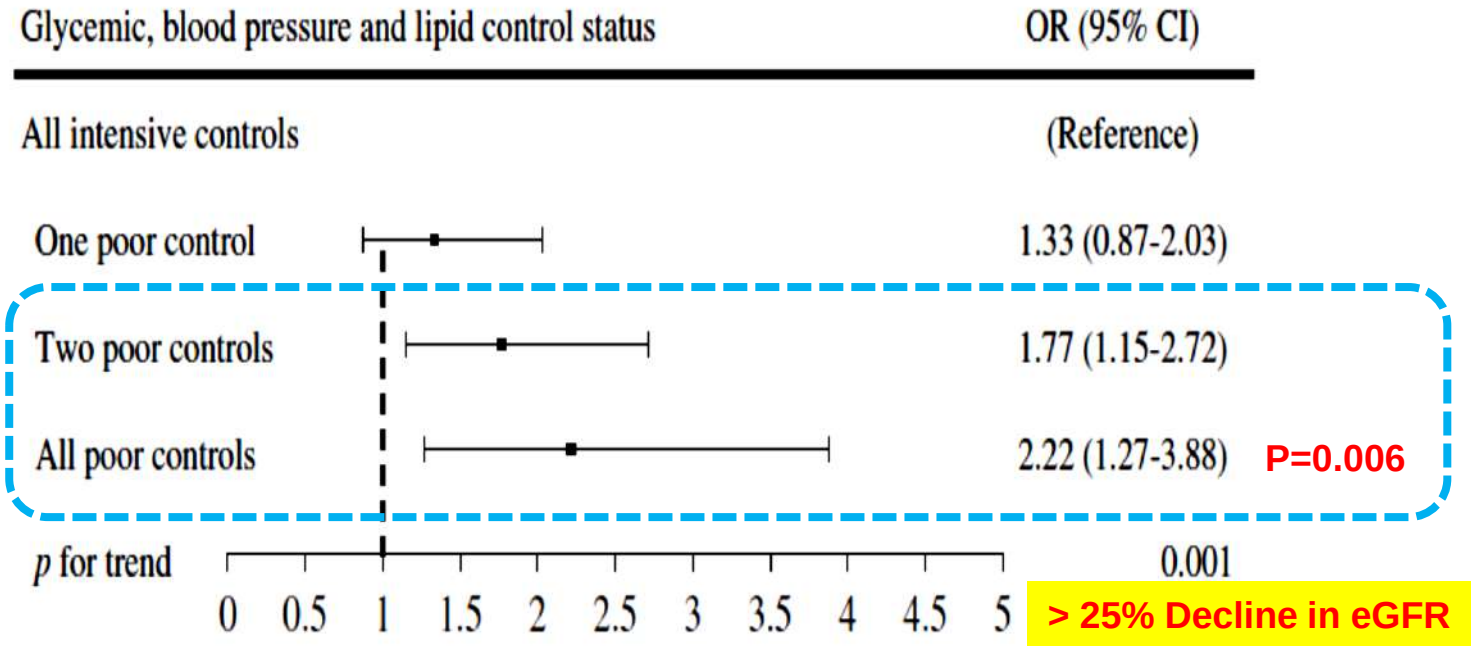
EKG & CxR: LVH, Urine ACR 4688, eGFR 56.8

我們能幫這病人做些什麼？

Simultaneous control of glycemic, blood pressure, and lipid significantly reduce the risk of renal progression in diabetes patients

Total of 1602 diabetes patients were included in the study analysis, the mean age was 63.03 ± 10.98 years, 55.56% were men. The study population was derived from eight hospitals in Taiwan from October 2008 to April 2015. Demographic characteristics were collected using structured questionnaires. Clinical variables were obtained from medical chart review. The renal progression was defined as a decline in the eGFR by more than 25% according to the baseline eGFR.

三高必須同時都控制好,才能有效減少腎臟病變的發生及惡化！



Comprehensive effects of glycemic, blood pressure and lipid controls on renal progression. Odds ratio was adjusted for covariate factors. The poor control of glycemic, blood pressure, and lipid was defined as HbA1C ≥ 7%, SBP ≥ 130 mm Hg, and total cholesterol ≥200 mg/dl, respectively.

Po-Ya Chang et al. (Taipei Medical University) European Journal of Internal Medicine 2016 (36): 87–92.

Deleting Death and Dialysis: Conservative Care of Cardio-Vascular Risk and Kidney Function Loss in Chronic Kidney Disease (CKD)

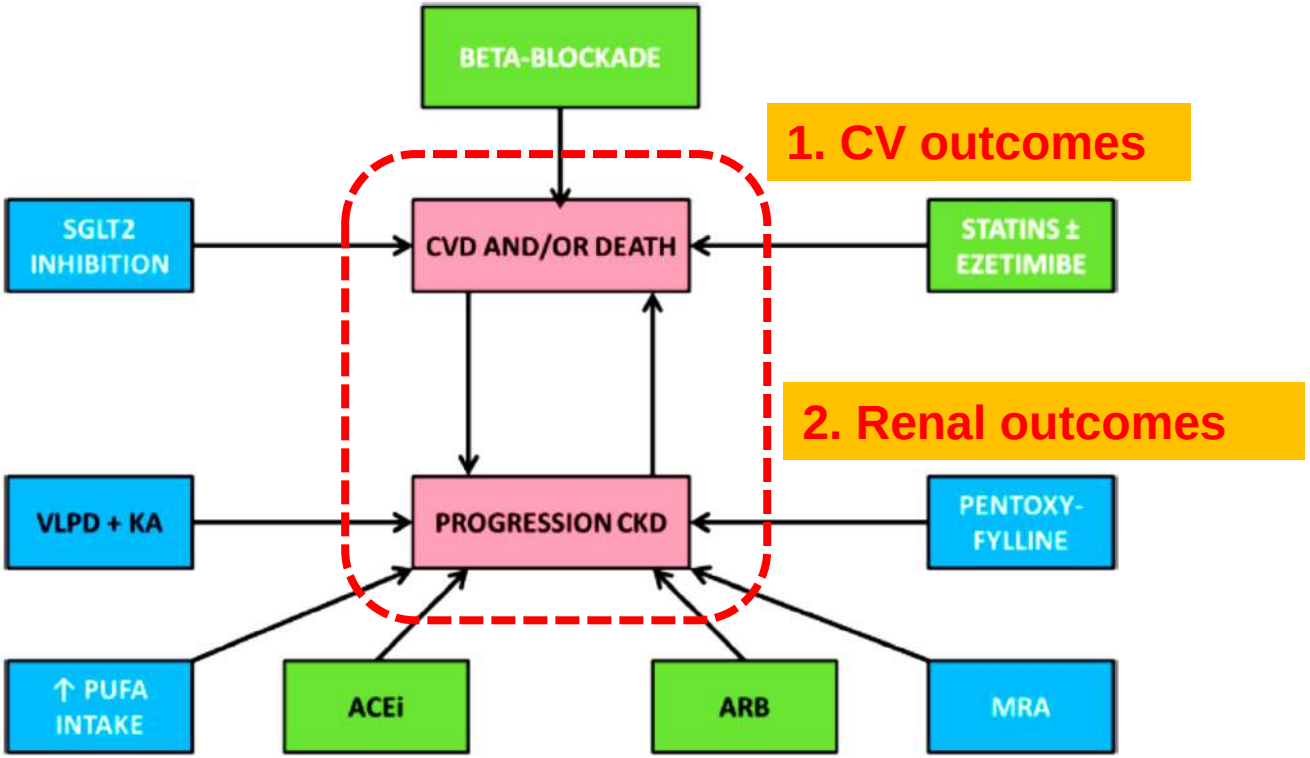


Figure 2. Main interventions with the potential to reduce cardio-vascular risk. Pink background: outcomes to be modified; green background: strong arguments in favor of a benefit (corresponding to +++ in the tables); blue background: suggestive arguments in favor of benefit (corresponding to

Raymond Vanholder et al. Toxins 2018, 10, 237; doi:10.3390/toxins10060237

Stop CKD progression
Clinical Evidence from individual trials

1) Hyperglycemia
2) Hypertension
3) Hyperlipidemia
4) Hyperuricemia
5) Proteinuria (Albuminuria)

心腎代謝症候群

CardioRenal Metabolic Syndrome !

治療目標

Treatment Targets:

- **J or U curve limits for item 1), 2), 4).**
- **The lower the better for item 3) and 5).**

6) **Protein-bound uremic toxins (colon microbiota- dysbiosis)**

(Oral adsorbents for preventing CVD and CKD progression)

Hyperglycemia and Chronic Kidney Disease

Glucose targets for preventing diabetic kidney disease and its progression (Review)

To evaluate the benefits and harms of intensive (HbA1c < 7% or fasting glucose levels < 120 mg/dL versus standard glycaemic control (HbA1c ≥ 7% or fasting glucose levels ≥ 120 mg/dL) for preventing the onset and progression of kidney disease among adults with diabetes.

Analysis 1.4. Comparison 1 Tight versus non-tight glycaemic control, Outcome 4 Cardiovascular mortality.

Review: Glucose targets for preventing diabetic kidney disease and its progression

Comparison: 1 Tight versus non-tight glycaemic control

Outcome: 4 Cardiovascular mortality

Study or subgroup	Tight n/N	Non-tight n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
VA-CSDM Study 1992	3/75	3/78		7.0 %	1.04 [0.22, 4.99]
MEMO Study 2011	3/89	4/89		7.7 %	0.75 [0.17, 3.25]
STENO-2 Study 1999	7/80	7/80		12.5 %	1.00 [0.37, 2.72]
VADT Study 2003	40/892	33/899		21.7 %	1.22 [0.78, 1.92]
ACCORD Study 2007	195/5128	94/5123		25.1 %	2.07 [1.63, 2.64]
ADVANCE Study 2001	253/5571	289/5569		26.0 %	0.88 [0.74, 1.03]
Total (95% CI)	**11835**	**11838**		**100.0 %**	**1.19 [0.73, 1.92]**

Total events: 501 (Tight), 430 (Non-tight)

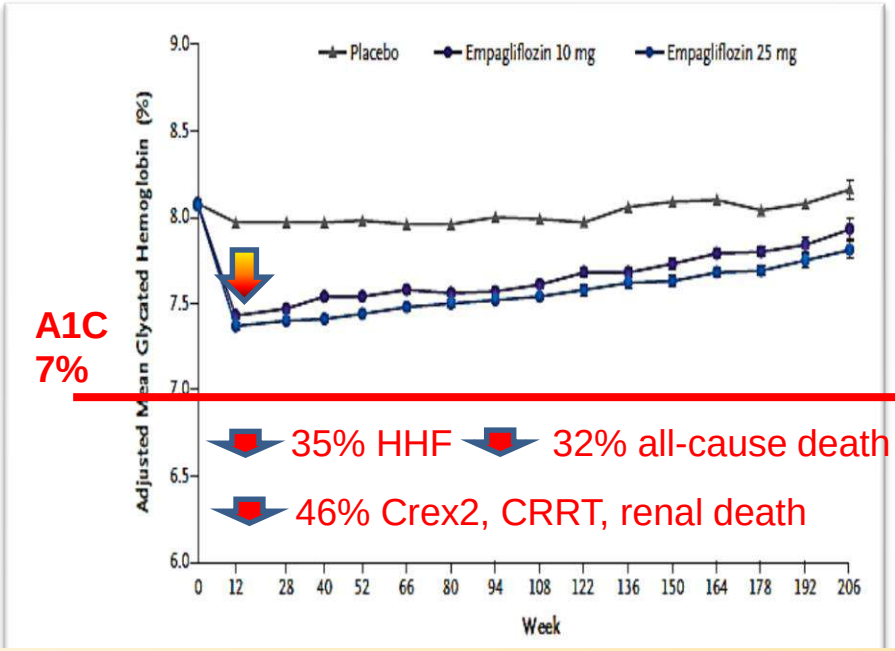
個人心得：

治療糖尿病，選擇對心腎保護有優越證據力的新藥物是非常重要的，其重要性甚至超越 **A1C** 的數值 **< 7%！**

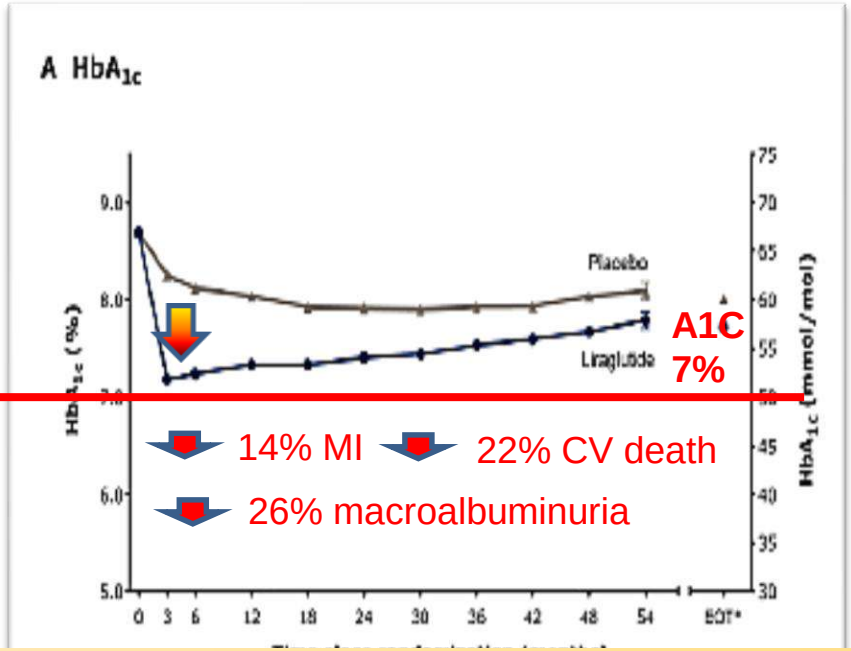
Ruospo M et al. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD010137. DOI: 10.1002/14651858.CD010137.pub2.

SGLT-2 inhibitors *vs.* GLP-1RA

EMPA-REG [1]



LEADER [2]



只要一開始選對降糖藥, 譬如 metformin 加上 SGLT-2 inhibitor 或 metformin 加上 GLP-1RA, 使用至少3個月以上, 曾經達成HbA1C < 7.5%, 對心腎功能就產生保護的 Legacy effetcs !

1. Christoph Wanner et al. NEJM 2016, June 14, DOI: 10.1056/NEJMoa1515920
2. Johannes F.E. Mann et al . N Engl J Med 2017;377:839-48.

Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus:

A Guidance Statement Update From the American College of Physicians

Guidance Statement 1: *Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.*

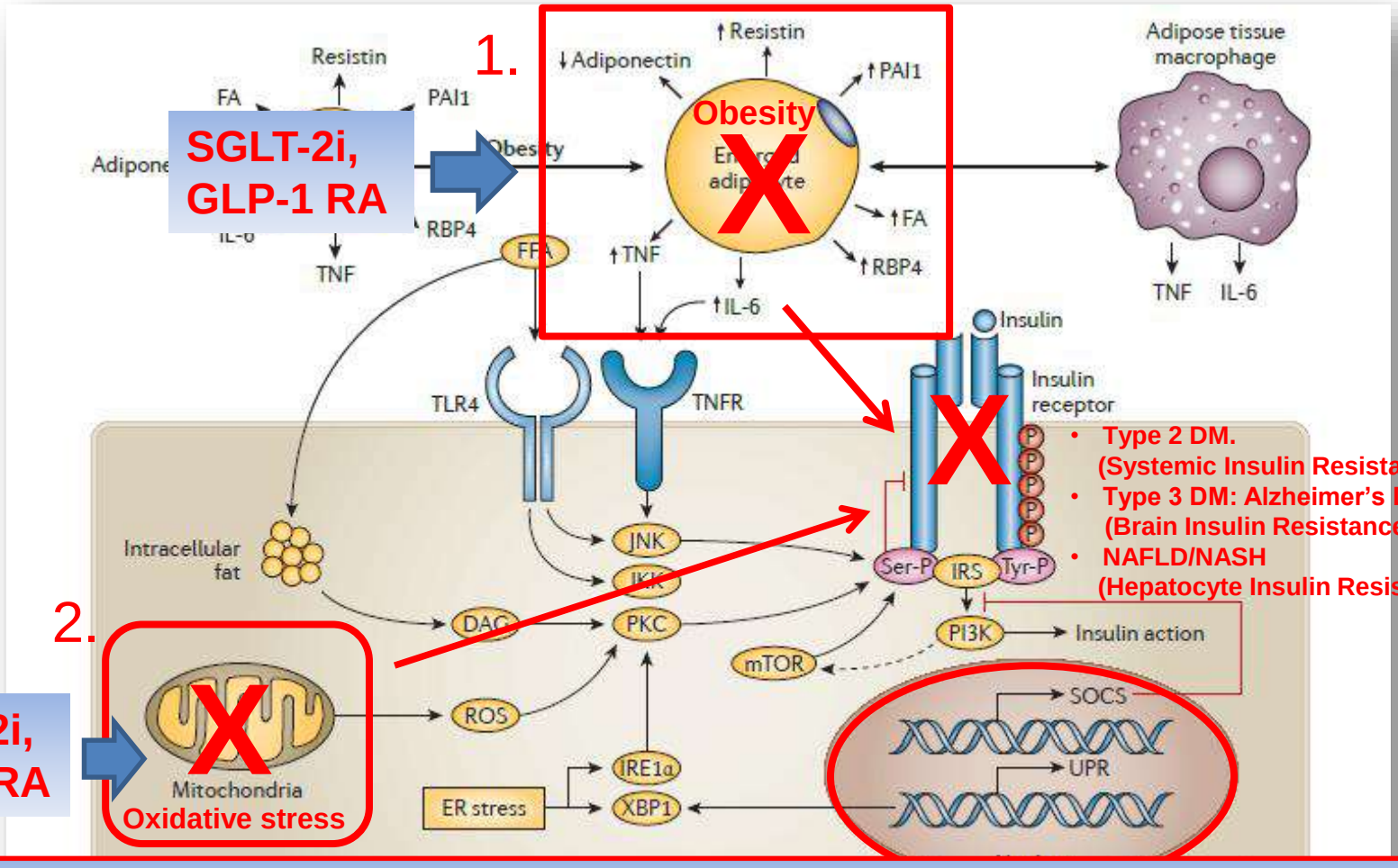
Guidance Statement 2: *Clinicians should aim to achieve an **HbA1c level between 7% and 8%** in most patients with type 2 diabetes.*

Guidance Statement 3: *Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.*

Guidance Statement 4: *Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.*

Amir Qaseem et al. Ann Intern Med. 2018;168:569-576.
Clinical Guidelines Committee of the American College of Physicians

Type 2 diabetes mellitus
- Mechanisms of Insulin Resistance



- Type 2 DM.
  (Systemic Insulin Resistance)
- Type 3 DM: Alzheimer's Disease
  (Brain Insulin Resistance)
- NAFLD/NASH
  (Hepatocyte Insulin Resistance)

SGLT-2i & GLP-1RA 能減重(脂肪)及減少糖尿病患體內細胞的 oxidative stress, 因而也能改善因胰島素阻抗性增加 (hyperinsulinemia)所而造成的器官傷害！

Ralph A. DeFronzo et al. NATURE REVIEWS 2015 Article number: 15019
doi:10.1038/nrdp.2015.19

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Renal outcomes:
Worsening renal function,
or ESRD,
or Renal death.

Meta-analysis of EMPA-REG, CANVUS, DECLARE

	EMPA-REG OUTCOME[2]	CANVAS Program[3]	DECLARE-TIMI 58[4]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10 142	17 160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3613 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

Table: Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors

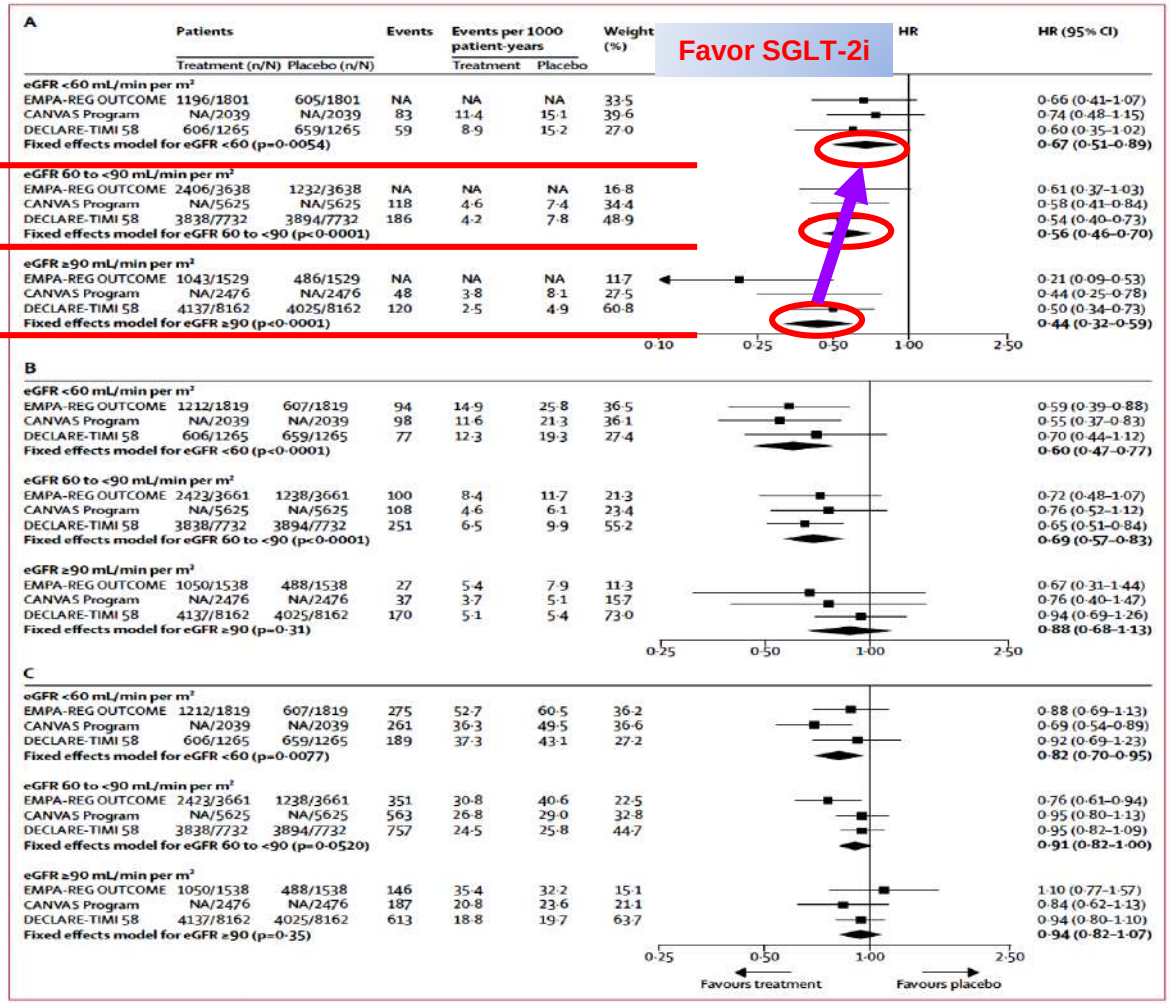


Figure 5: Meta-analysis of SGLT2i trials on the composite of worsening of renal function, end-stage renal disease, or renal death (A), hospitalisation for heart failure (B), and major adverse cardiovascular events stratified by the eGFR levels (C)

Thomas A Zelniker et al. (TIMI group) The Lancet 2018 November 10;
http://dx.doi.org/10.1016/S0140-6736(18)32590-X.

Dapagliflozin slows the progression of the renal and liver fibrosis associated with type 2 diabetes

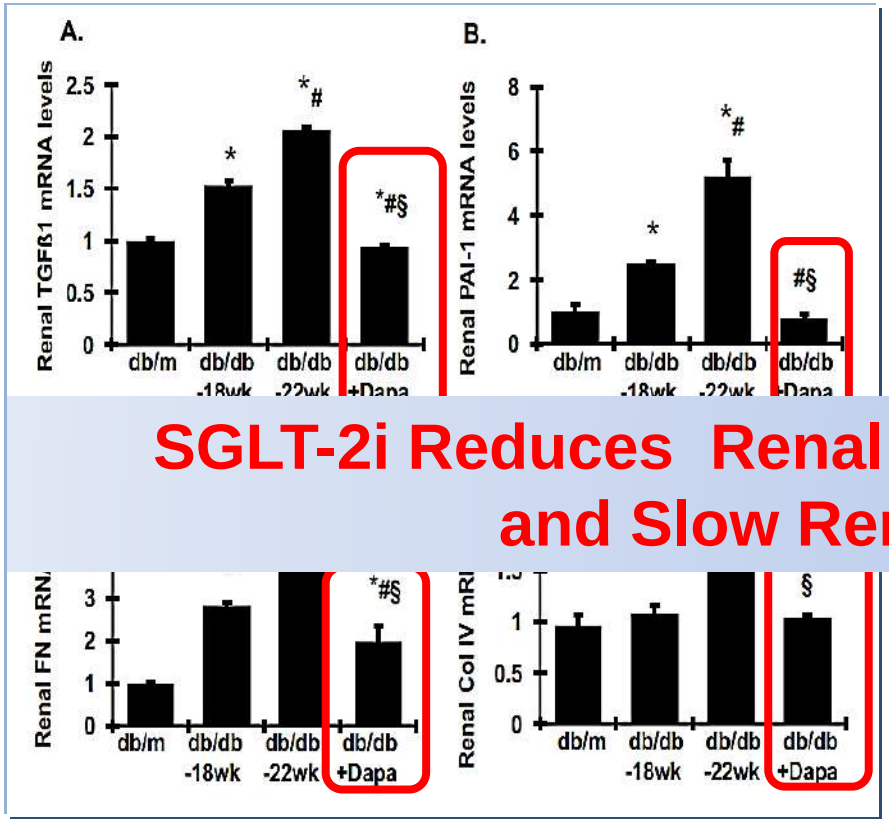


Figure 3. Effect of dapagliflozin on renal mRNA expression of fibrotic markers.

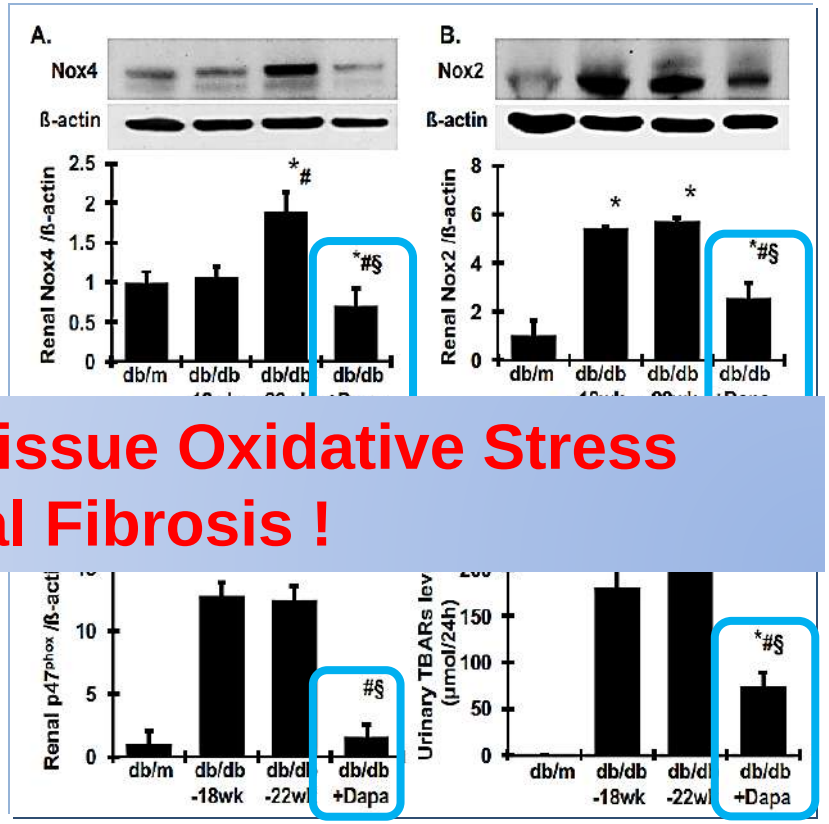


Figure 6. Effect of dapagliflozin on protein production of renal NAPDH oxidases and renal TBARS levels.

SGLT-2i Reduces Renal Tissue Oxidative Stress and Slow Renal Fibrosis !

Li Tang et al. Am J Physiol Endocrinol Metab (August 15, 2017). doi:10.1152/ajpendo.00086.2017

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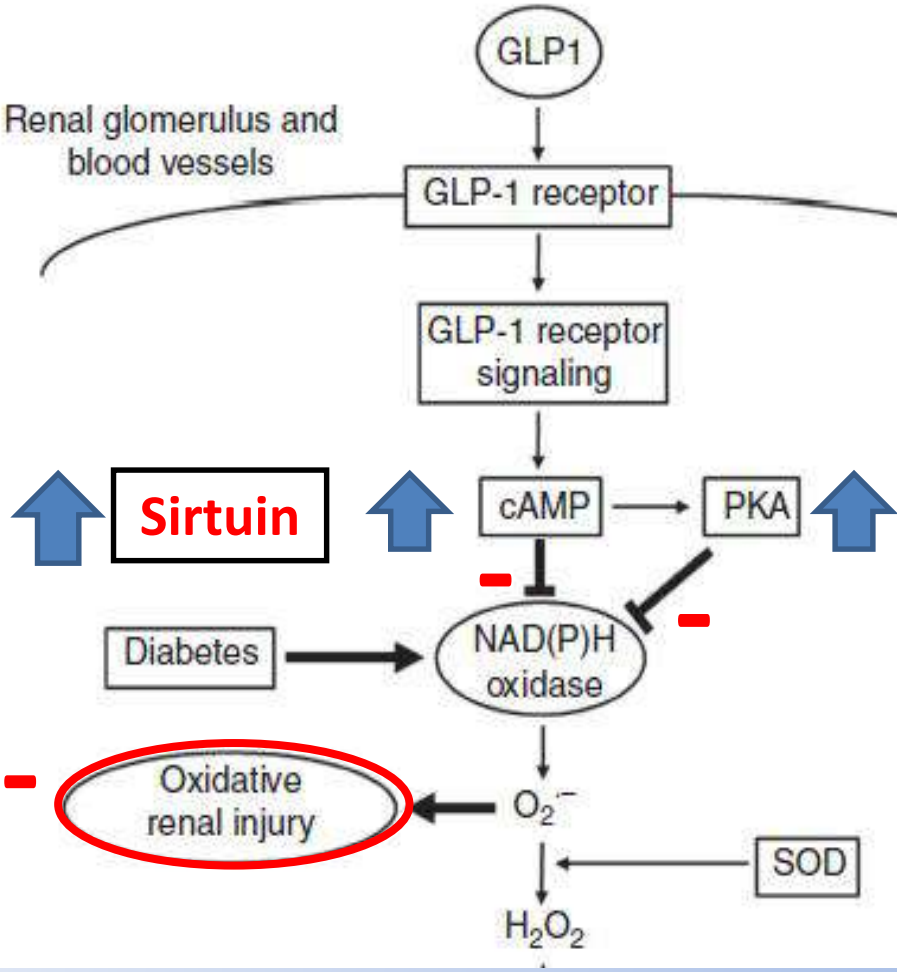
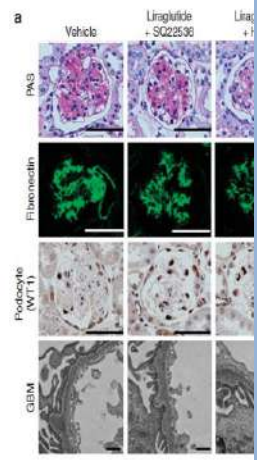
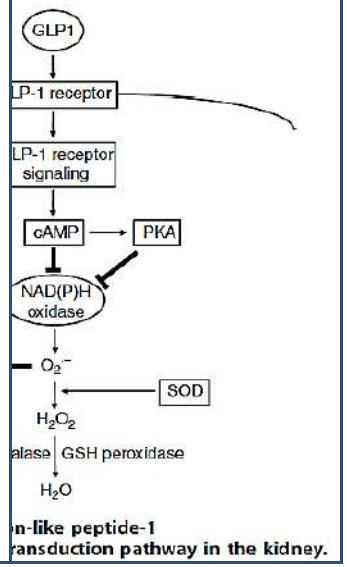


GLP-1 在腎臟細胞結合 GLP-1R之後，產生抗發炎及 抗過氧化傷害的保護作用！

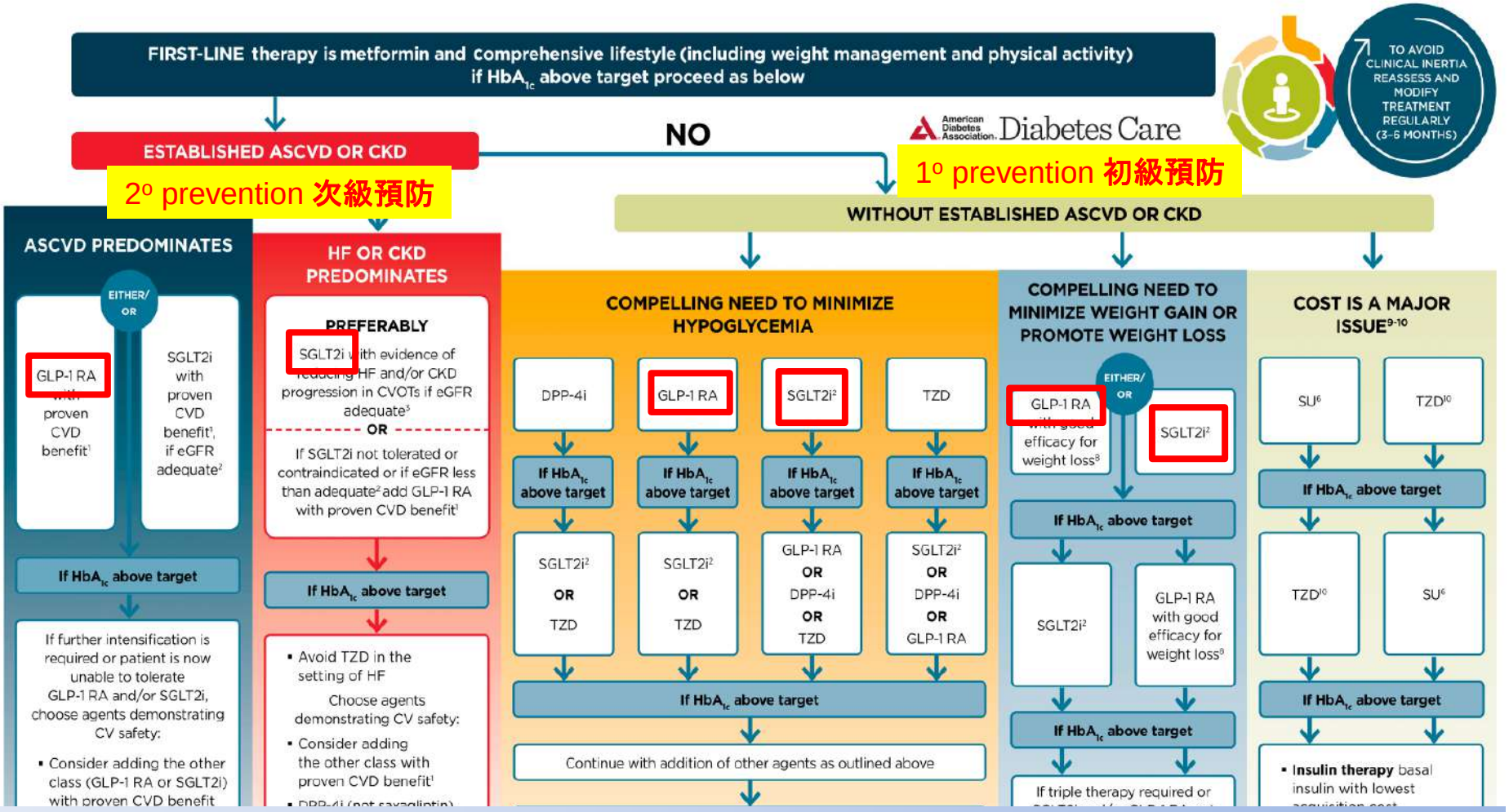
Figure 10 | Proposed glucagon-like peptide-1 receptor–dependent signal-transduction pathway in the kidney.





AMERICAN DIABETES ASSOCIATION (ADA)

STANDARDS OF MEDICAL CARE IN DIABETES -- 2019



- **SGLT-2 inhibitors are superior in preventing heart failure and ESRD.**
- **GLP-1RAs are superior in preventing ASCVD and proteinuric CKD.**

Diabetes Care 2019 Jan; 42 (Supplement 1)

Hypertension and Chronic Kidney Disease

Which BP target achieved
can prevent CV /all-cause mortality or
renal progression to ESRD in patients
with Chronic Kidney Disease

Evidences support

BP goal < (140/90 ~130/80) mmhg, (ACEI /ARB/CCB)

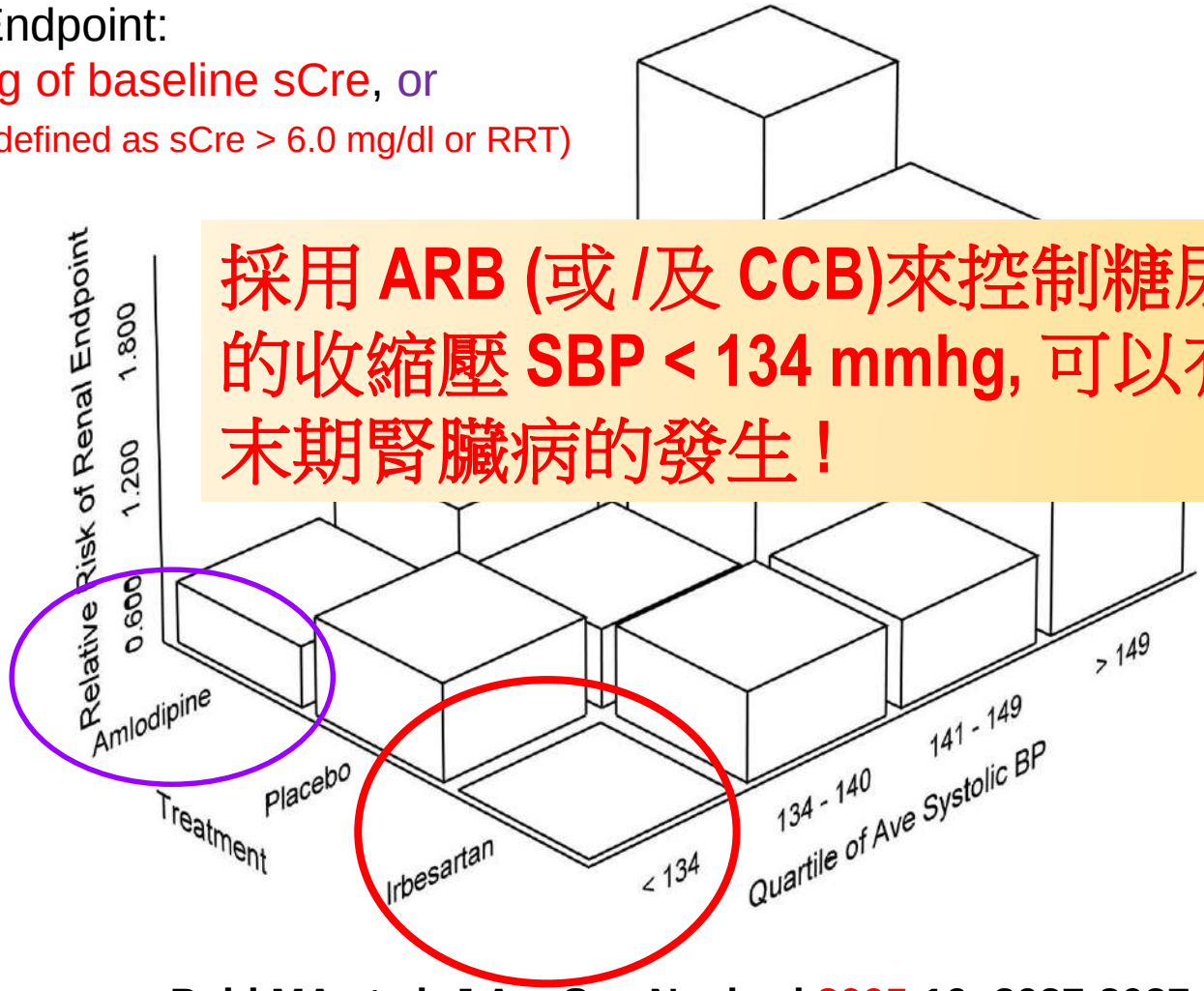
and reduce Blood Pressure Variability, (CCB)

but not sBP < 110 mmhg.

Independent and Additive Impact of Blood Pressure Control and Angiotensin II Receptor Blockade on Renal Outcomes in the Irbesartan Diabetic Nephropathy Trial (IDNT)

Entry criteria included elevated baseline serum creatinine concentration up to 266 umol/L(3.0mg/dl) and urine protein excretion >900 mg/d. Baseline BP averaged 159/87 ± 20/11mmHg. Median patient follow-up was 2.6 yr.

Renal Endpoint:
Doubling of baseline sCre, or
ESRD (defined as sCre > 6.0 mg/dl or RRT)



採用 ARB (或 /及 CCB)來控制糖尿病病患的收縮壓 SBP < 134 mmhg, 可以有效減少末期腎臟病的發生！

Pohl MA et al. J Am Soc Nephrol 2005;16: 3027-3037.

Independent and Additive Impact of Blood Pressure Control and Angiotensin II Receptor Blockade on Renal Outcomes in the Irbesartan Diabetic Nephropathy Trial (IDNT)

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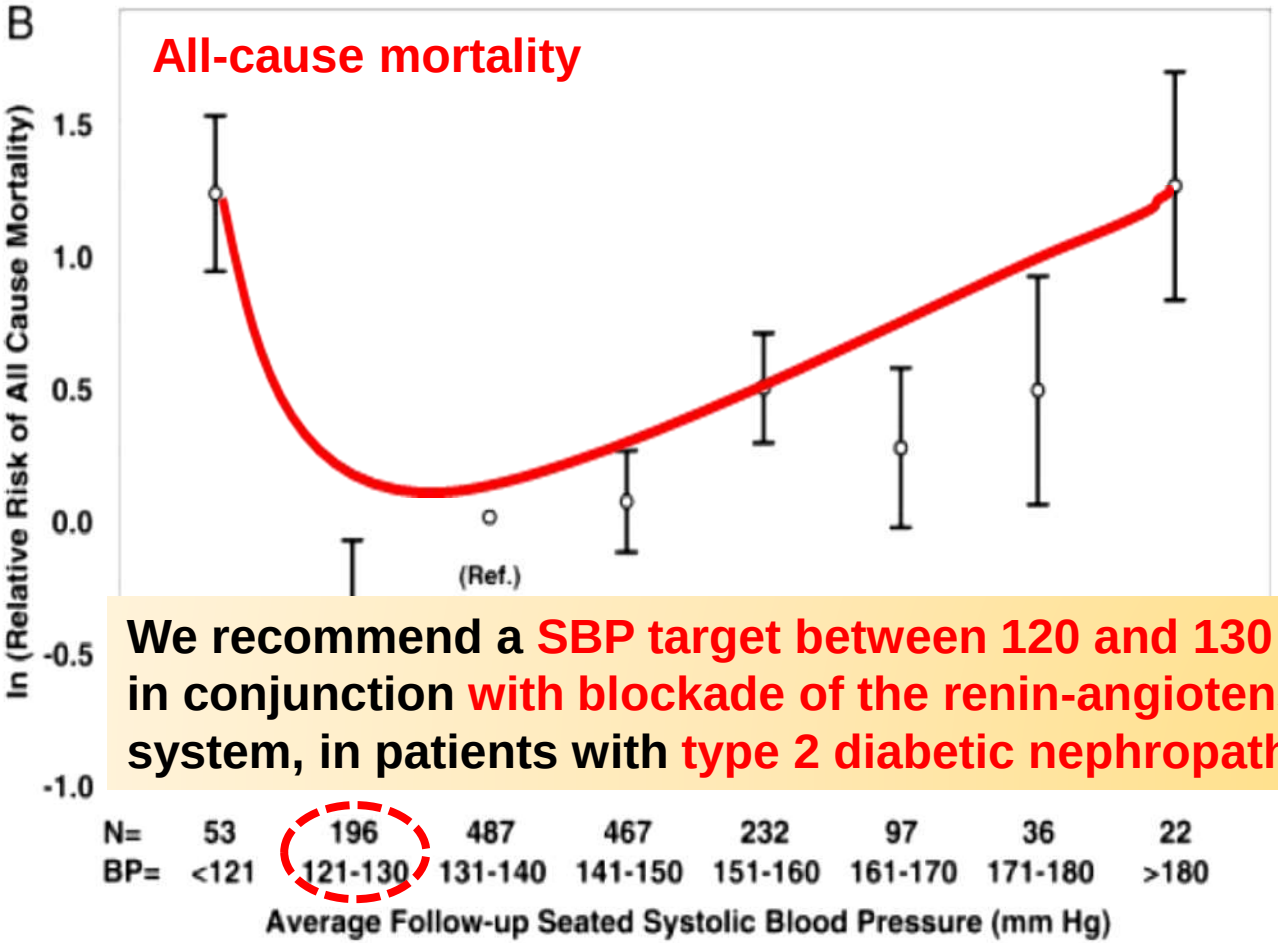


We recommend a SBP target between 120 and 130 mmHg, in conjunction with blockade of the renin-angiotensin system, in patients with type 2 diabetic nephropathy.

Pohl MA et al. J Am Soc Nephrol 2005;16: 3027-3037.

SBP 110 ~120 mmhg may be the lowest BP target for CKD patients to reduce the risk for renal disease progression, regardless of proteinuria.

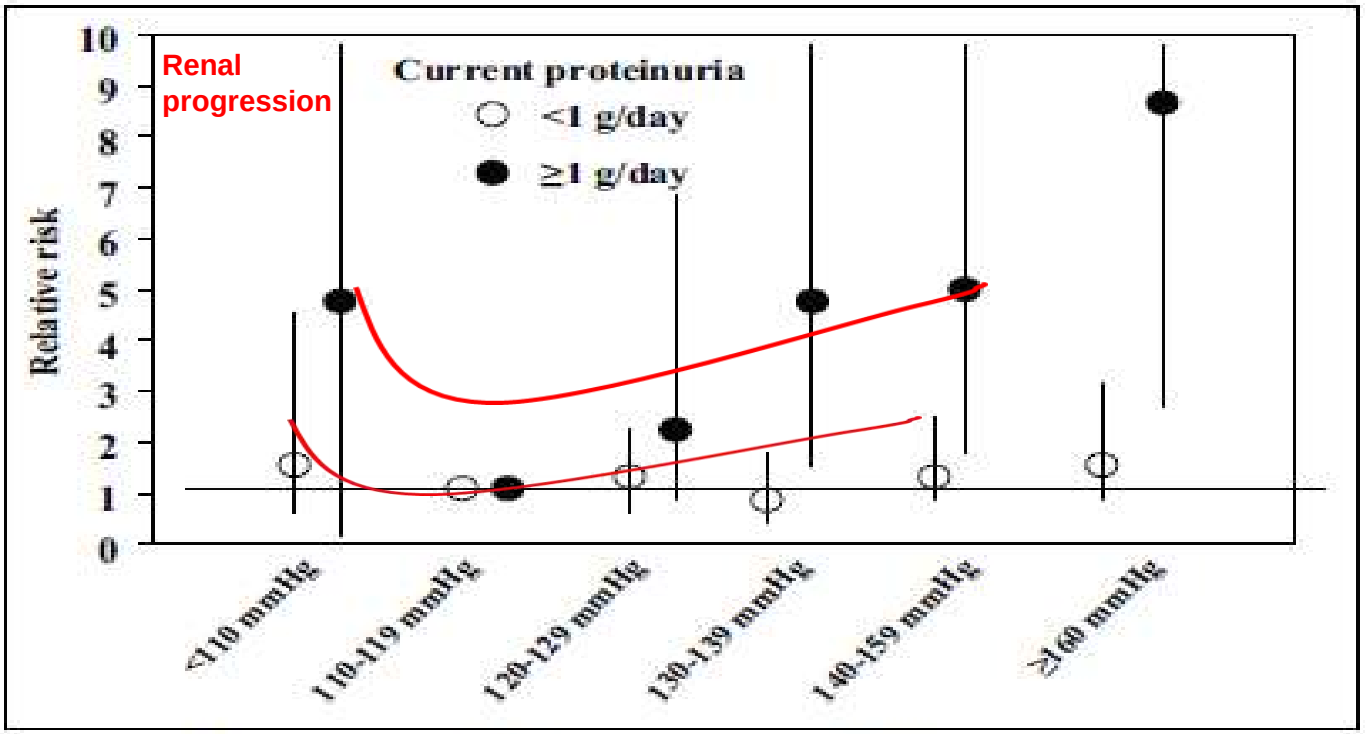
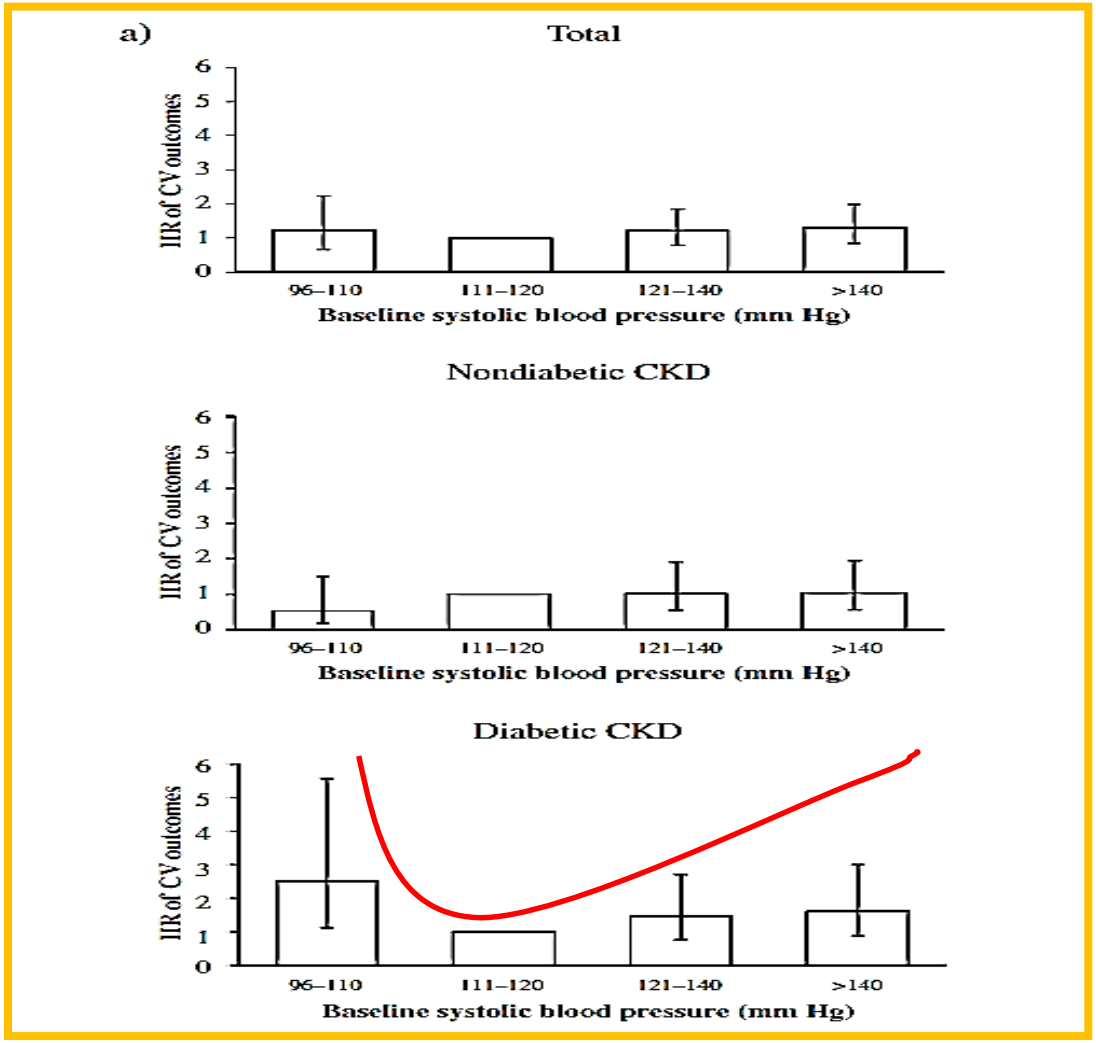


Figure 1) *The relative risk for kidney disease progression based on current systolic blood pressure and urine protein excretion. The relative risk for patients with a current protein excretion of 1.0 g/day or more represents 9336 patients (223 events), and the relative risk for patients with a current urine protein excretion of less than 1.0 g/day represents 13,274 patients (88 events). Modified from reference 9*

Jafar TH et al. AIRPD study group. Ann Intern Med 2003;139:244-52

Systolic Blood Pressure and Cardiovascular Outcomes in Stage 3~4 Chronic Kidney Disease Patients: Evidence from a Taiwanese Cohort （高雄醫學大學附設醫院）

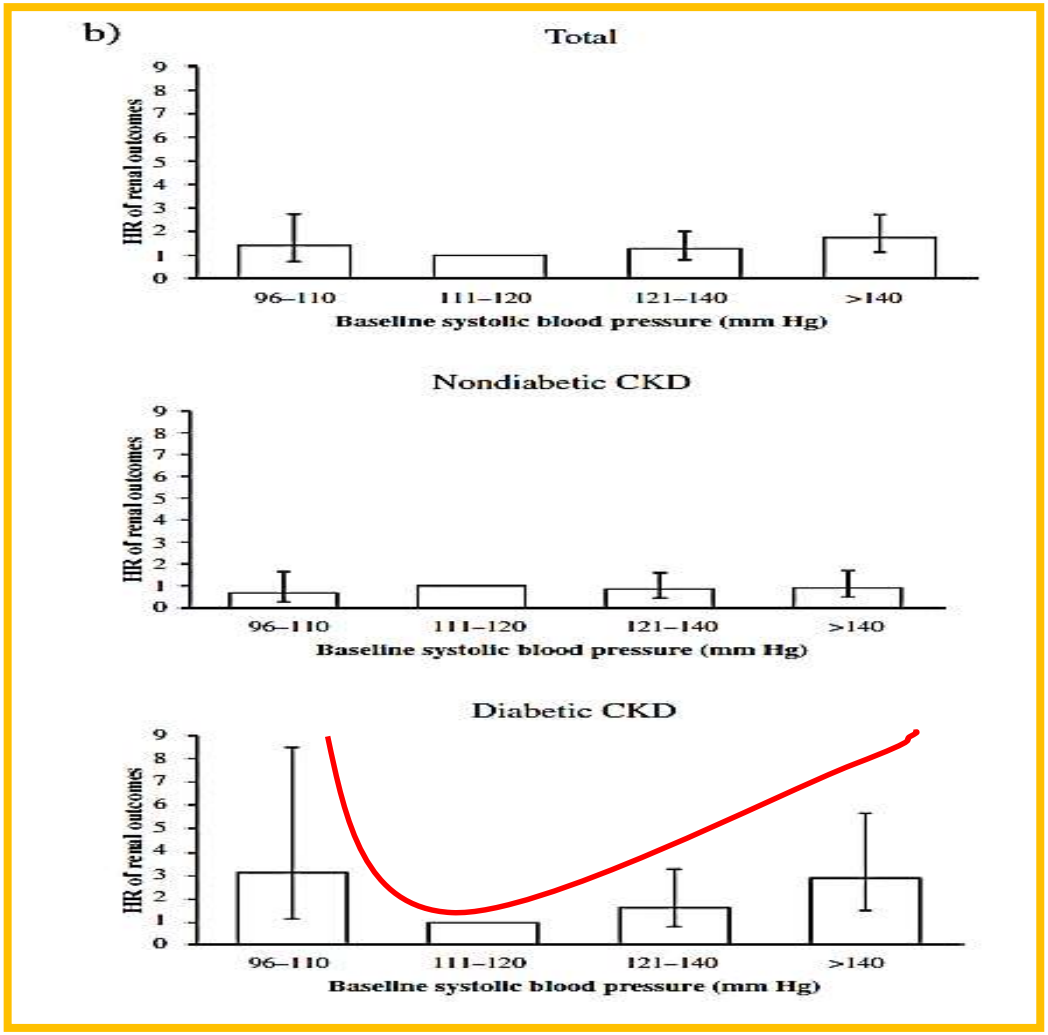
CV outcomes



Heng-Pin Chiang et al. American Journal of Hypertension 2014; 27(11): 1396 -1407

Systolic Blood Pressure and Renal Outcomes in Stage 3~4 Chronic Kidney Disease Patients: Evidence from a Taiwanese Cohort （高雄醫學大學附設醫院）

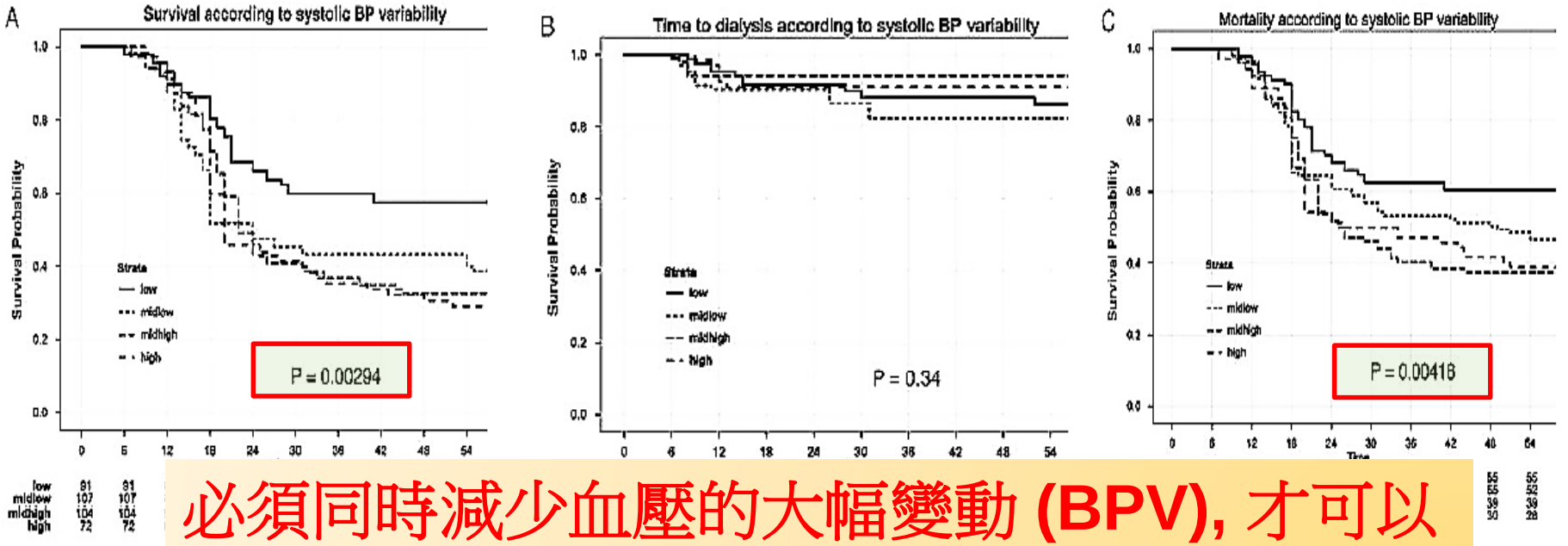
Renal outcomes



Heng-Pin Chiang et al. American Journal of Hypertension 2014; 27(11): 1396 -1407

Visit-to-Visit Blood pressure variability (BPV) and outcomes in chronic kidney disease

- A longitudinal retrospective, observational, multi-center study in three tertiary care nephrology outpatient clinics (54 weeks).



必須同時減少血壓的大幅變動 **(BPV),** 才可以有效地減少 **CKD** 病患的死亡率！

Fig. 1. Time-to-death (A), dialysis (B) and death even after dialysis initiation (carry-over effect) (C) according to the systolic BPV.

Biagio Di Iorio et al. Nephrol Dial Transplant (2012) 27: 4404–4410

2015 臺灣慢性腎臟病 臨床診療指引

罹患糖尿病的慢性腎臟病病人的血壓處理原則

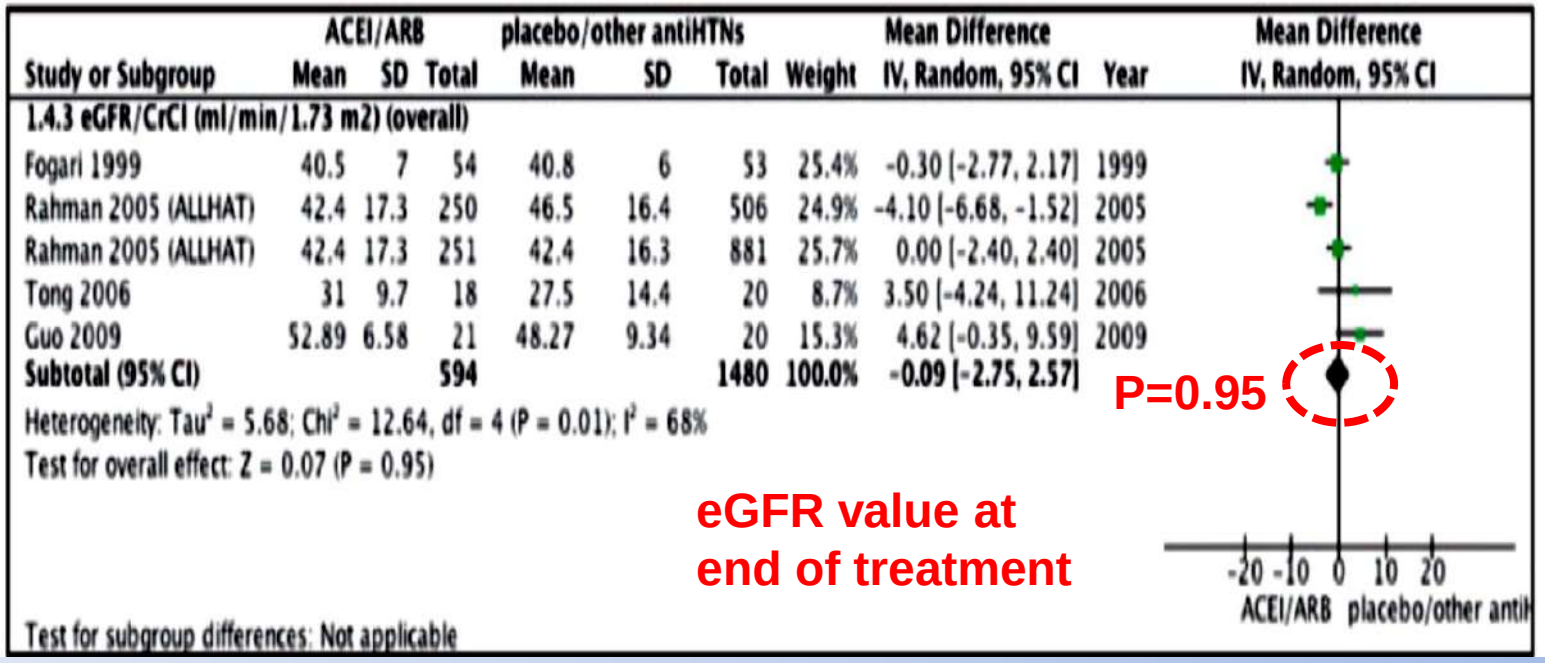
建議強度	建議內容	證據等級	文獻編號
B	CKD 合併糖尿病、但不需透析且尿中白蛋白每天＜ 30 mg 者，建議維持收縮壓≦ 140 mmHg 且舒張壓≦ 90 mmHg。	1++ 4	17,62-67 79
B	CKD 合併糖尿病且出現白蛋白尿（含微量白蛋白尿）病人且血壓超過 130/80 mmHg 時，建議使用降血壓藥物。	1- 2++ 1++ 1+	80, 83,85,87 84 86
B	建議 CKD 合併糖尿病出現微量白蛋白尿者，治療使用 ACEi 或 ARB。	1++ 1+ 1-	92,93,96,101,102 27,99,100 94-95,97
A	建議 CKD 合併糖尿病且出現大量白蛋白尿者，治療使用 ACEi 或 ARB。	1++	89-91,

For example:
1st ARB plus 2nd CCB to achieve safe BP target, reduce BP variability, reduce proteinuria, and to improve CV and Renal outcome !

財團法人國家衛生研究院 發行

Effect of renin–angiotensin–aldosterone system blockade in adults with diabetes mellitus and advanced chronic kidney disease not on dialysis: a systematic review and meta-analysis

We conducted a meta-analysis of randomized controlled trials (RCTs) of at least 6-months duration in adult patients with diabetes who also have non-dialysis CKD stages 3–5.



Study or Subgroup	ACEI/ARB Mean	SD	Total	placebo/other antiHTNs Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.4.3 eGFR/CrCl (ml/min/1.73 m2) (overall)									
Fogari 1999	40.5	7	54	40.8	6	53	25.4%	-0.30 [-2.77, 2.17]	1999
Rahman 2005 (ALLHAT)	42.4	17.3	250	46.5	16.4	506	24.9%	-4.10 [-6.68, -1.52]	2005
Rahman 2005 (ALLHAT)	42.4	17.3	251	42.4	16.3	881	25.7%	0.00 [-2.40, 2.40]	2005
Tong 2006	31	9.7	18	27.5	14.4	20	8.7%	3.50 [-4.24, 11.24]	2006
Guo 2009	52.89	6.58	21	48.27	9.34	20	15.3%	4.62 [-0.35, 9.59]	2009
Subtotal (95% CI)			**594**			**1480**	**100.0%**	**-0.09 [-2.75, 2.57]**	

Heterogeneity: $Tau^2 = 5.68$; $Chi^2 = 12.64$, df = 4 (P = 0.01); $I^2 = 68\%$

Test for overall effect: Z = 0.07 (P = 0.95)

Test for subgroup differences: Not applicable

eGFR value at end of treatment

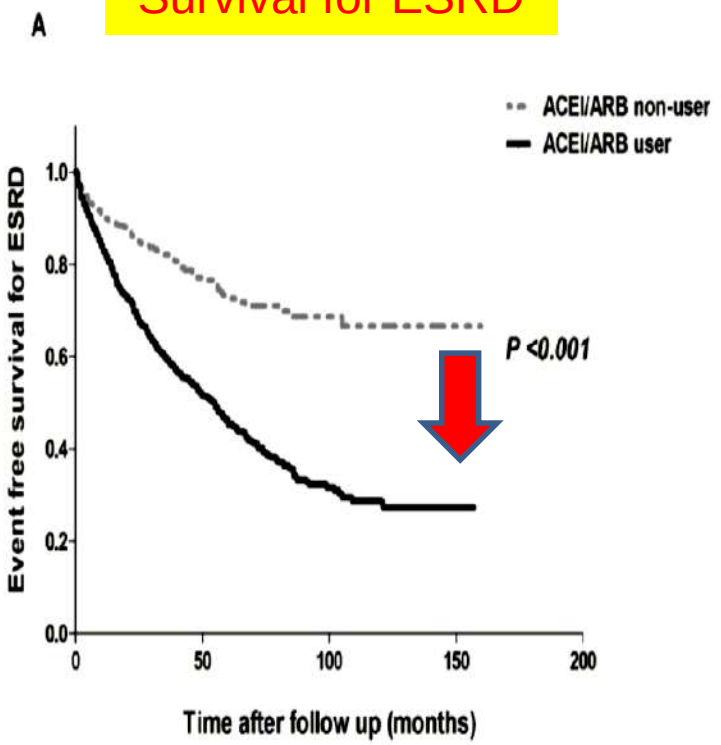
- We found evidence that in patients with diabetes mellitus and CKD stages 3–5, treatment with RAAS-blocking agents did not result in a clear survival advantage.
- We did not find evidence that the use of RAAS blocking agents expedited the need for RRT in patients with CKD stages 3–5.

Ionut Nistor et al. Nephrol Dial Transplant 2018 (33): 12–22.

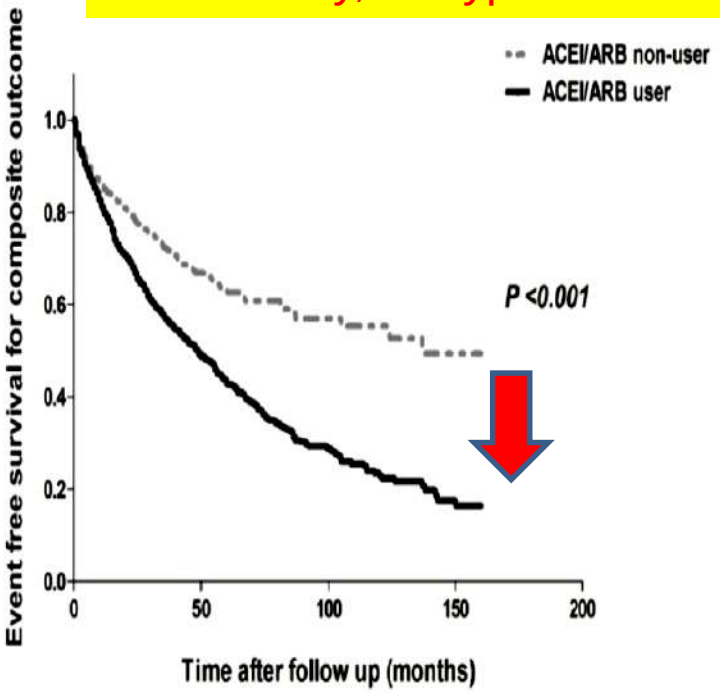
The Impact of Renin-Angiotensin System Blockade on Renal Outcomes and Mortality in Pre-Dialysis Patients with Advanced Chronic Kidney Disease (CKD stage 4 or 5, eGFR < 30 ml/min/1.73m^2).

This was a retrospective propensity score (PS)-matched study on the effects of RAS blockers on renal outcomes and/or death in pre-dialysis patients with severe advanced CKD (stage 4 or 5, eGFR < 30 ml/min/1.73m^2). A total of 2,076 advanced CKD patients were included in the analysis

Survival for ESRD



Survival for ESRD, or all-cause mortality, or hyperkalemia



The habitual use of RAS blockades in pre-dialysis patients with advanced CKD may have a detrimental effect on renal outcome without improving all-cause mortality.

Yun Jung Oh et al. PLoS ONE 2017; 12 (1): e0170874.

Angiotensin-converting enzyme inhibitors or angiotensin receptor blocker monotherapy retard deterioration of renal function in Taiwanese chronic kidney disease population

We conducted a multicentre, longitudinal cohort study based on the Epidemiology and Risk Factors Surveillance of CKD database from 2008 to 2013; the database is maintained separately by the Bureau of Health Promotion, Ministry of Health and Welfare, Taiwan. Totally 2639 patients with CKD and hypertension were enrolled in this study. We included 217 participants, 1405 participants, and 1017 participants in the ACEI monotherapy group, the ARB monotherapy group, and the control group, respectively. Among these patients, **1217 had early-stage CKD (CKD stage 1, stage 2, and stage 3a) and 1422 had advanced CKD (CKD stage 3b, stage 4, and stage 5)**. **We defined the progression of renal deterioration by an average eGFR decline of more than 5 mL/min/1.73 m2/yr or the commencement of dialysis**.

Type of Treatment	Study Outcome, OR (95% CI)			
	Unadjusted	*p*-value	Adjusted	*p*-value
ACEI/ARB user (n = 1622)	0.79 (0.67–0.94)	0.0095	0.79 (0.63–0.99)	0.0405
ACEI monotherapy (n = 217)	0.73 (0.52–1.02)	0.0677	0.83 (0.49–1.41)	0.4888
ARB monotherapy (n = 1405)	0.80 (0.67–0.96)	0.0174	0.85 (0.67–1.09)	0.2127
Nonuser (n = 1017)	1	–	1	–

Table 3. Study Outcomes: Risk in Patients with CKD Stages 1–5 and Hypertension

單獨服用**ACEI** 或單獨服用 **ARB**, 並無法有效阻止腎功能惡化！

Cai-Mei Zheng et al. Scientific Reports (2019) 9:2694

The impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease

52 patients (21 females and 31 males) with advanced CKD (stages 4 and 5), who attended our low clearance clinic (LCC) in preparation for renal replacement therapy (RRT). Mean age was 73.3 ± 1.8 years with an estimated glomerular filtration rate (eGFR) of 16.38 ± 1 ml/min/1.73 m2. Baseline urine protein:creatinine ratio (PCR) was 77 ± 20 mg/mmol. 46% suffered from diabetes mellitus. Patients were followed for at least 12 months before and after ACEi/ARB were stopped.

Table 2. Comparisons of clinical variables between groups

	12 months before ACEi/ ARB were stopped	When ACEi/ARB were stopped	12 months after ACEi/ ARB were stopped	Significance
SBP (mmHg)		134 ± 3 mmHg	139 ± 2.2 mmHg	$P = 0.04$
DBP (mmHg)		69 ± 1.7 mmHg	72 ± 1.4 mmHg	$P = 0.04$
MAP (mmHg)		90 ± 1.8 mmHg	94 ± 1.3 mmHg	$P = 0.02$
Urine Protein:creatinine ratio (PCR) (mg/mmol)	79.5 ± 24.1 mg/mmol	77 ± 20 mg/mmol	121.6 ± 33.6 mg/mmol	NS
Urine PCR for diabetics	97.5 ± 36.2 mg/mmol	110.4 ± 38.3 mg/mmol	135.7 ± 48.2 mg/mmol	NS
Urine PCR for non-diabetics	62.2 ± 32.5 mg/mmol	51.3 ± 16 mg/mmol	108 ± 47.6 mg/mmol	NS

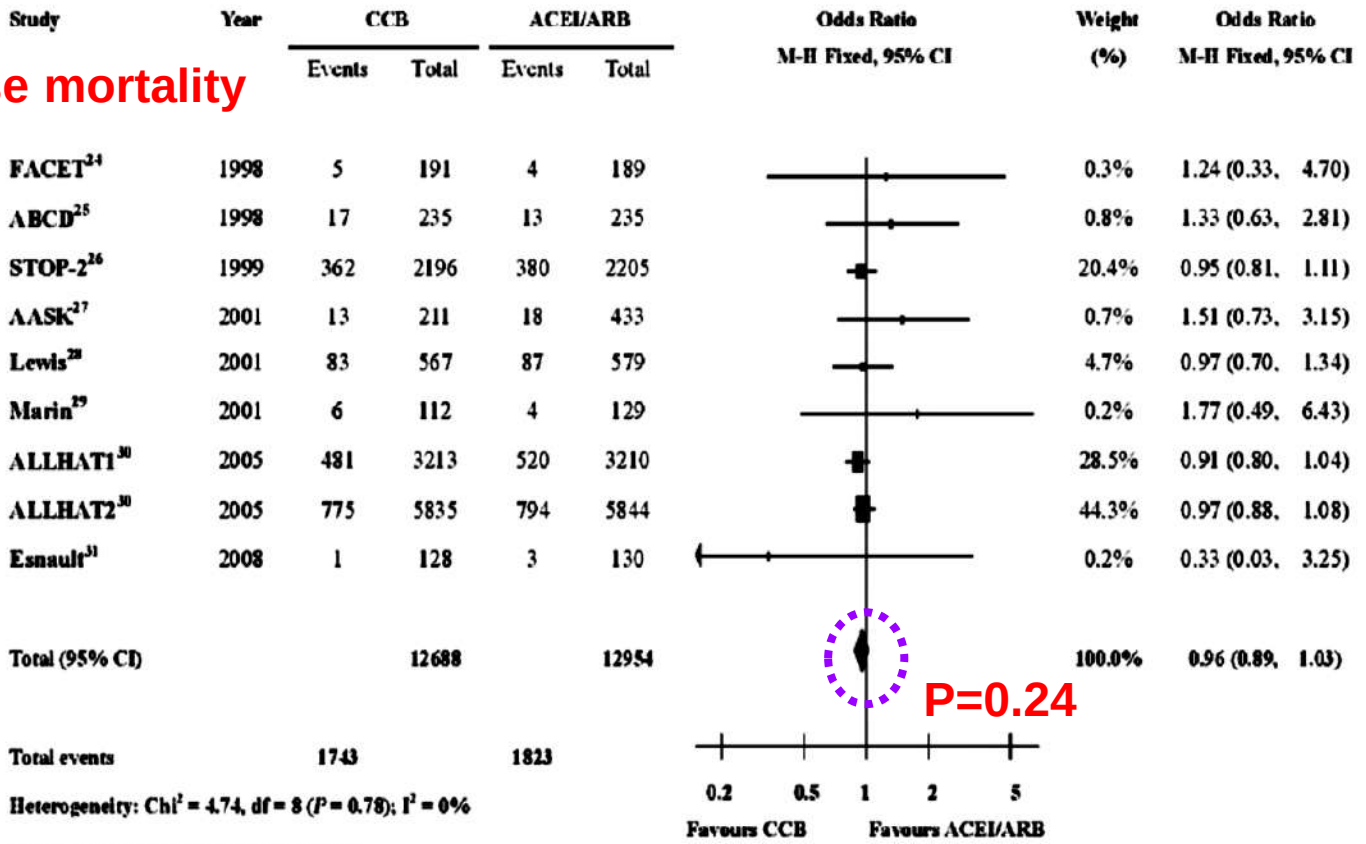
Conclusion:

Discontinuation of ACEi/ARB has undoubtedly delayed the onset of RRT in the majority of those studied. This observation may justify a rethink of our approach to the inhibition of the RAAS in patients with advanced CKD who are nearing the start of RRT.

Aimun K. Ahmed et al. Nephrol Dial Transplant (2010) 25: 3977–3982.

Effect of calcium channels blockers and inhibitors of the renin-angiotensin system on renal outcomes and mortality in patients suffering from chronic kidney disease: systematic review and meta-analysis

All-cause mortality



Conclusions:

CCBs did not increase all-cause mortality incidence in patients with CKD though they displayed weaker renoprotective, compared to ACEIs or ARBs therapy.

Hong-Jin Zhao et al. Renal Failure, 2016; 38:6, 849-856.

2016 nephron Clinical Practice

Clinical Practice: Review

Nephron 2016;133:147–158
DOI: 10.1159/000447068

Received: January 16, 2016
Accepted after revision: May 18, 2016
Published online: June 24, 2016

Should We STOP Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers in Advanced Kidney Disease? (Stage 4-5 CKD)

Nephrol Dial Transplant (2015) 0: 1–7
doi: 10.1093/ndt/gfv346

ndt Nephrology Dialysis Transplantation

Original Article

Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial

Sunil Bhandari[1,2], Natalie Ives[3], Elizabeth A. Brettell[3], Marie Valente[3], Paul Cockwell[4], Peter S. Topham[5], John G. Cleland[6], Arif Khwaja[7] and Meguid El Nahas[7]

[1]Department of Renal Medicine, Hull and East Yorkshire Hospitals NHS Trust, Kingston upon Hull, UK, [2]Hull York Medical School, East

AEEI / ARB 用於 eGFR < 30 或 eGFR 急速下降的病患身上,
個人建議劑量應減半再減半, 甚至停藥觀察 eGFR 之變化,
並改以(CCB ± vasodilator ± diuretic)取代做為降血壓藥物！

ACEi/ARB treatment can stabilize or even improve renal function in patients with advanced progressive CKD.

Methods. The STOP-ACEi trial (trial registration: current controlled trials, ISRCTN62869767) is an investigator-led multicentre open-label, randomized controlled clinical trial of 410 participants with advanced (Stage 4 or 5) progressive CKD receiving ACEi, ARBs or both. Patients will be randomized in a 1:1 ratio to either discontinue ACEi, ARB or combination of both (experimental arm) or continue ACEi, ARB or combination of both (control arm). Patients will be followed up at 3 monthly intervals for 3 years. The primary outcome measure is eGFR at 3 years. Secondary outcome measures include the number of renal events, participant quality of life and physical functioning, hospitalization rates, BP and laboratory measures, including serum cystatin-C. Safety will be assessed to ensure

Keywords: angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), chronic kidney disease, eGFR, randomized controlled trial

INTRODUCTION

Chronic kidney disease (CKD), Stages 3–5, affects 1 in 10 adults in the UK and reflects progressive scarring of the kidneys regardless of the original disease and is associated with a high prevalence of cardiovascular disease [1]. Advanced CKD (Stage 4 or 5) is associated with a significantly increased risk of death [hazard ratio (HR): 3.6; 95% confidence interval (CI) 3.2–4.0] [2] and a 50-fold increased requirement for dialysis, in comparison with age-matched individuals with presumed normal kidney function [3–6]. Advanced CKD has a major negative impact on a range of other clinical outcomes including quality of life [7, 8] and carries a high economic burden either through

Hypertension management and renin-angiotensin-aldosterone system blockade in patients with diabetes, nephropathy and/or chronic kidney disease

When should RAAS blockade be stopped ?

a. **Hyperkalaemia**
   1. **not to offer these agents if the patient's pre-treatment serum potassium > 5 mmol/l**
   2. **these agents should be stopped if the serum potassium > 6 mmol/l.**

b. **A drop in eGFR by 25% or an increase in serum creatinine by 30% or more**

c. **Pregnancy**

d. **Inter-current illness**

   There are risks of large reductions in eGFR with RAAS blockade, particularly during intercurrent illness or with intravascular fluid depletion (diarrhoea, vomiting and high fever). It is therefore recommended to reduce the dose or to hold off ACEI or ARB use until recovery is made.

These precautions should especially be taken if a patient is on a **combination** involving **non-steroidal anti-inflammatory drugs** and/or **diuretics/SGLT-2 i** !

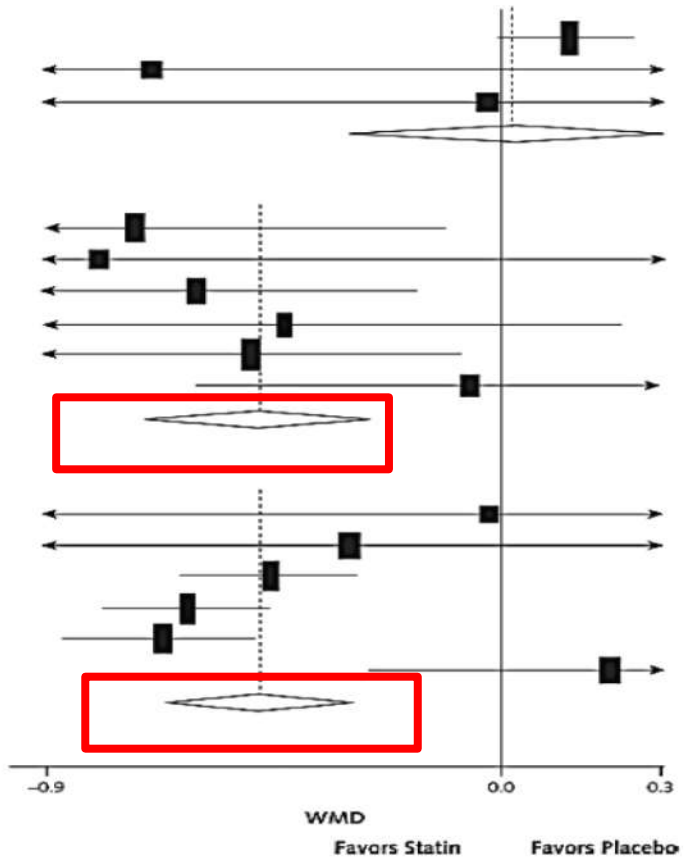
Indranil Dasgupta et al. ABCD-The Renal Association 2017 Hypertension Guideline.

Hyperlipidemia and Chronic Kidney Disease

Meta-Analysis: The Effect of Statins on Albuminuria

Figure 2. Individual and pooled results of 15 randomized, placebo-controlled trials examining the effect of statins on albuminuria or proteinuria, stratified by baseline excretion.

Study, Year (Reference)	Statin	Sample Size, *n*	Effect (95% CI), %
Excretion < 30 mg/d			
Asselbergs et al., 2004 (18)	Pravastatin	864	12 (–1 to 25)
Dalla Nora et al., 2003 (20)	Atorvastatin	25	–70 (–171 to 31)
Fried et al., 2001 (21)	Simvastatin	39	–5 (–90 to 81)
Subtotal of WMD			2 (–32 to –35)
Excretion, 30–299 mg/d			
Buemi et al., 2000 (19)	Fluvastatin	21	–73 (–136 to –10)
Lintott et al., 1995 (26)	Fluvastatin	42	–81 (–217 to 55)
Nakamura et al., 2001 (28)	Cerivastatin	60	–61 (–106 to –16)
Nielsen et al., 1993 (29)	Simvastatin	18	–44 (–113 to 25)
Tonolo et al., 1997 (31)	Simvastatin	20	–50 (–93 to –7)
Zhang et al., 1995 (32)	Pravastatin	20	–8 (–61 to 45)
Subtotal of WMD			–48 (–71 to –25)
Excretion ≥ 300 mg/d			
Hommel et al., 1992 (22)	Simvastatin	21	–5 (–137 to 128)
Lam et al., 1995 (23)	Lovastatin	36	–32 (–102 to 38)
Lee et al., 2002 (25)	Pravastatin	66	–47 (–64 to –29)
Lee et al., 2005 (24)	Pravastatin	82	–62 (–79 to –45)
Nakamura et al., 2002 (27)	Cerivastatin	40	–67 (–87 to –48)
Thomas et al., 1993 (30)	Simvastatin	30	20 (–28 to 67)
Subtotal of WMD			–47 (–67 to –26)



Residual statistical heterogeneity: $I^2 = 23\%$ ($P = 0.27$) for excretion < 30 mg/d; $I^2 = 0\%$ ($P = 0.64$) for excretion of 30 to 299 mg/d; and $I^2 = 63\%$ ($P = 0.020$) for excretion ≥ 300 mg/d. WMD = weighted mean difference in the proportional change from baseline to follow-up albuminuria (or proteinuria) between statin and placebo groups.

Kevin Douglas et al. Ann Intern Med. 2006;145:117-124

HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis (Stage 1~5ND CKD)

Statin versus placebo or no treatment for adults with chronic kidney disease not on dialysis

Patient or population: adults with chronic kidney disease
Settings: not on dialysis
Intervention: statin
Comparison: placebo or no treatment

Favor Statin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk per year treated			
	Placebo or no treatment	Statins			
Major cardiovascular events (MACE)	20 per 1000	14 per 1000 (13 to 16 per 1000) 6 fewer (4 to 7 fewer)	RR 0.72 (0.66 to 0.79)	36,033 (13)	⊕⊕⊕⊕ high
All-cause mortality	25 per 1000	20 per 1000 (17 to 23 per 1000) 5 fewer (2 to 8 fewer)	RR 0.79 (0.69 to 0.91)	28,276 (10)	⊕⊕⊕⊕ high
Cardiovascular mortality (CV mortality)	15 per 1000	12 per 1000 (10 to 13 per 1000) 3 fewer (2 to 5 fewer)	RR 0.77 (0.69 to 0.87)	19,059 (7)	⊕⊕⊕◯ moderate

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio

Suetonia C Palmer1 et al. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD007784.

Lowering cholesterol with statin in chronic kidney disease:

MACE

CKD stage

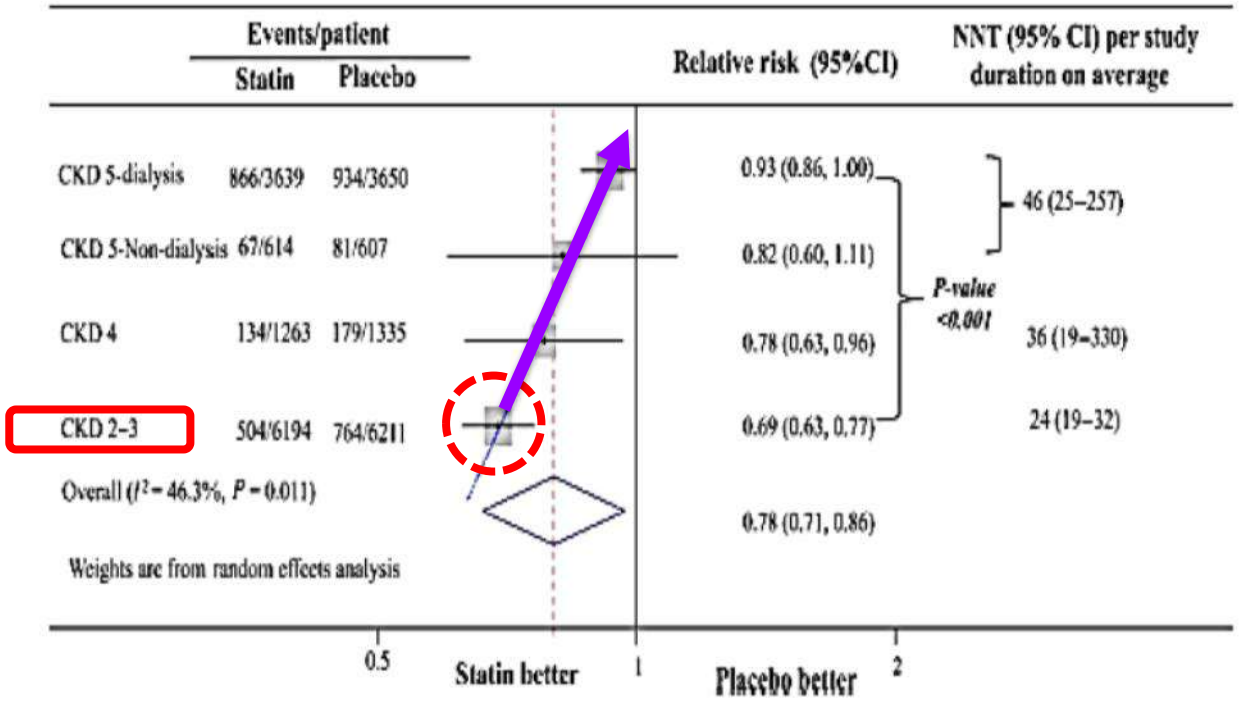
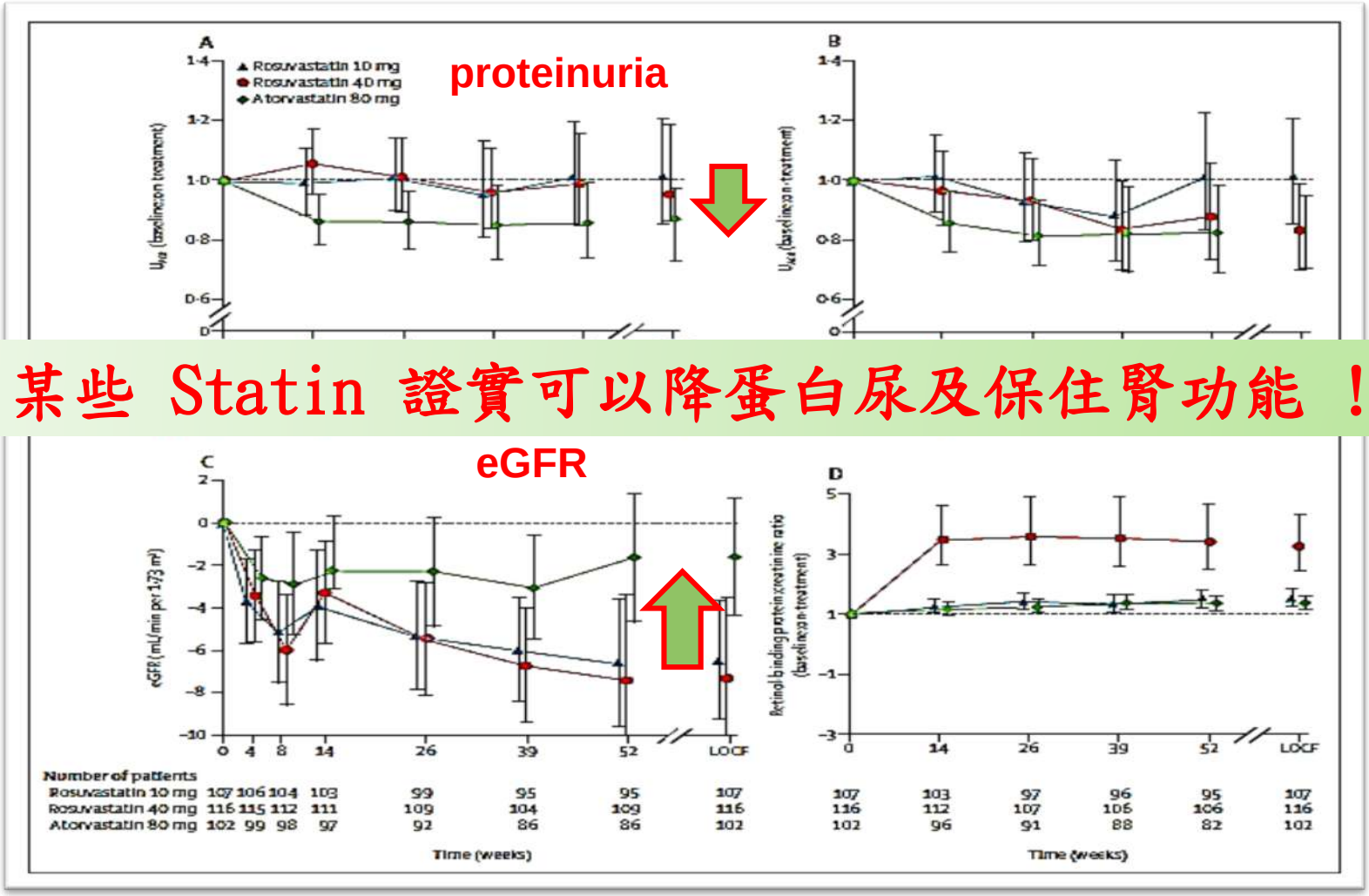


Figure 2 Effects of statin therapy on major cardiovascular events stratified by kidney function and the number needed to treat of statins in patients with chronic kidney disease. An decreased effects of statin therapy was observed with highest relative risk reduction seen in early chronic kidney disease, which becomes less pronounced as chronic kidney disease progressed. Chronic kidney disease stage 5: estimated GFR <15 mL/min/1.73 m^2, stage 4: estimated glomerular filtration rate 15–30 mL/min/1.73 m^2, stage 3: estimated glomerular filtration rate 30–60 mL/min/1.73 m^2, and stage 2: estimated glomerular filtration rate 60–90 mL/min/1.73 m^2. NNT, number need to treat.

Statin 在 CKD 越早期使用 (stage 1-3), 心血管保護效果越好！

Muh GeotWong et al. European Heart Journal (2015) 36, 2988–2995

Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial



某些 Statin 證實可以降蛋白尿及保住腎功能 !

Dick de Zeeuw et al. Lancet Diabetes Endocrinol. Published Online February 4, 2015
http://dx.doi.org/10.1016/S2213-8587(14)70246-3

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – 2018 EXECUTIVE SUMMARY

Table 1
AACE Lipid Targets for Patients with T2D (188,189,197,200,240-251)

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	≥2 risk factors and 10-year risk >10% or CHD risk equivalent[c], including diabetes or CKD 3, 4 with no other risk factors	<100	<130	<90
Moderate risk	≥2 risk factors and 10-year risk <10%	<130	<160	NR
Low risk	≤1 risk factor	<160	<190	NR

AACE/ACE Consensus Statement. ENDOCRINE PRACTICE Jan. 2018 Vol 24(No. 1).

2017台灣高風險病人血脂異常臨床治療指引

疾病 / 狀態	低密度膽固醇 (LDL-C) 之目標
急性冠心症候群	< 70 mg/dL
急性冠心症候群+ 糖尿病	< 55 mg/dL 可以考慮
穩定冠狀動脈疾病	< 70 mg/dL
缺血性腦中風或暫時性腦部缺氧	< 100 mg/dL
糖尿病	< 100 mg/dL
糖尿病+心血管疾病	< 70 mg/dL
慢性腎臟病(階段 3a–5, eGFR < 60)	> 100 mg/dL 時開始治療
家族性高膽固醇血症 (HeFH)	成人: < 100 mg/dL 小孩: < 135 mg/dL 有心血管疾病: < 70 mg/dL

根據 meta-analysis, 在 stage 1~3 CKD 就該開始治療！

Taiwan's LIPID Guidelines for Chronic Kidney Disease

2015 (財團法人國家衛生研究院)

建議強度	建議內容	證據等級	文獻編號
D	並無證據顯示，非藥物治療如運動、飲食調整、減少酒精攝取有助於高血脂症 CKD 病人的預後改善；欲有效降低血中 LDL-C，除改變生活習慣外，大部分仍需藥物治療。	1- 1+ 2++ 4	47-51,55-60 52-53 54,61 8
A	以降血脂藥物 statin 治療，減少心血管事件發生的效益，主要出現在第 1-4 期 CKD 病人。目前證據顯示，於透析開始後才使用 statin 治療無助於改善長期血液透析病人預後。	1- 1+	62-63 64-65,20
A	第 1-5 期 CKD 病人如果起始治療時 LDL-C ≥ 100mg/dL，可藉生活形態的改變或使用 statin，使血液中 LDL-C 下降，有助於降低心血管疾病風險；但以上建議不適用透析病人。	2++ 1+ 1++	13 20,23,64-65 21
D	CKD 病人接受降血脂治療的原則，須依照腎功能如 Ccr 或 eGFR 調整劑量，以及所選用的藥物動力特性來調整劑量。	4	39
D	目前無臨床證據顯示，statin 可提供 CKD 病人降低 LDL-C 以外的心臟血管保護效果。	4 2++	66 67
B	部分大型研究中，statin 並未讓 CKD 病人發生橫紋肌溶解症及肝功能異常的比率提高，但仍應小心使用。	1+	20,64-65

臺灣慢性腎臟病診療指引

Hyperuricemia and Chronic Kidney Disease

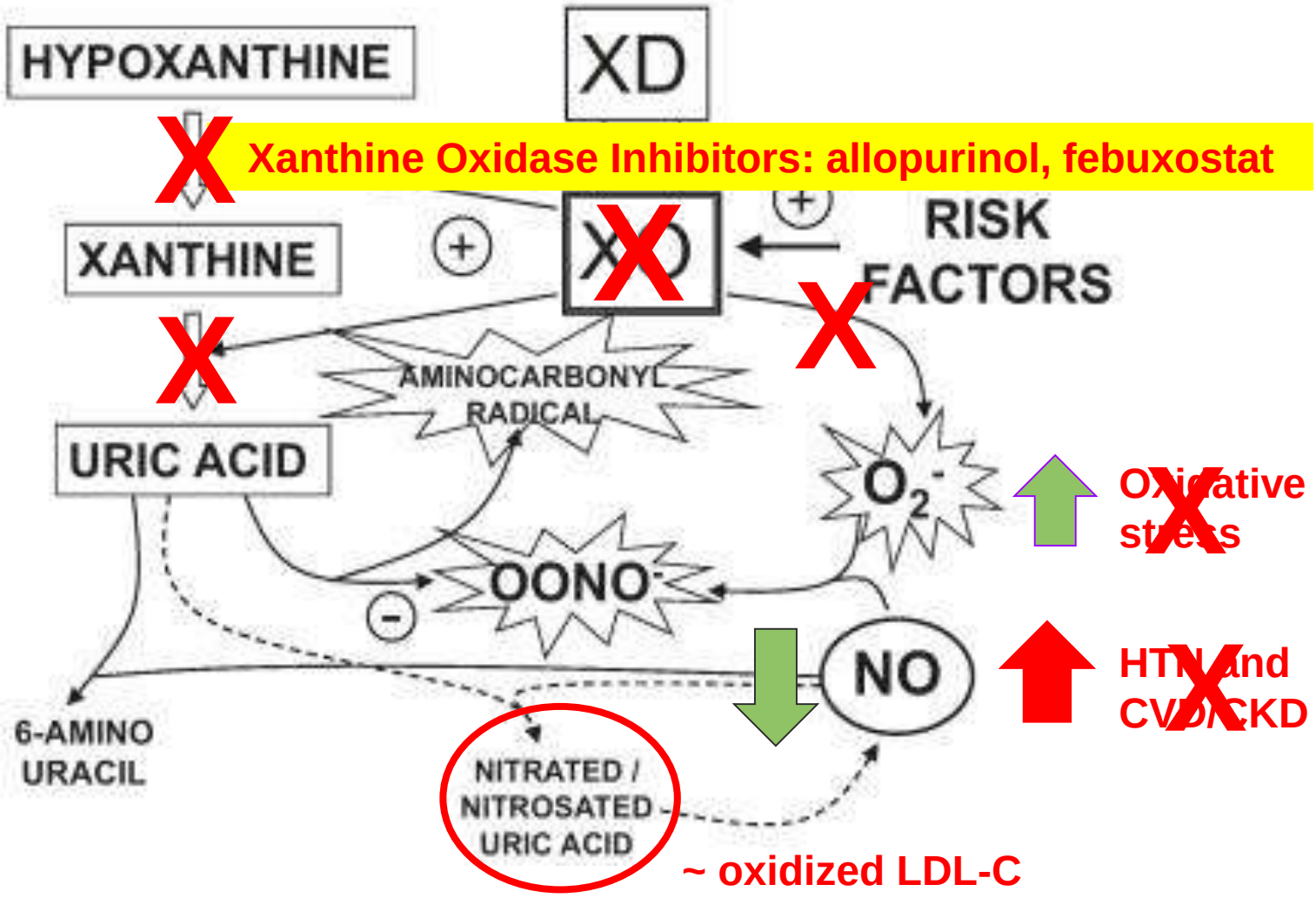
Effect of serum uric acid level on cardiovascular mortality

- NHANES showed a U-shaped association between cardiovascular mortality and serum uric acid level [1]. The risk of cardiovascular mortality was high for males with serum uric acid levels lower than 5.0 mg/dl and for females with serum uric acid levels lower than 4.0 mg/dl.

- Suliman et al. reported a J-shaped association between mortality and low serum uric acid levels (lower than 5.3 mg/dl) in patients with CKD stage 5 [2].

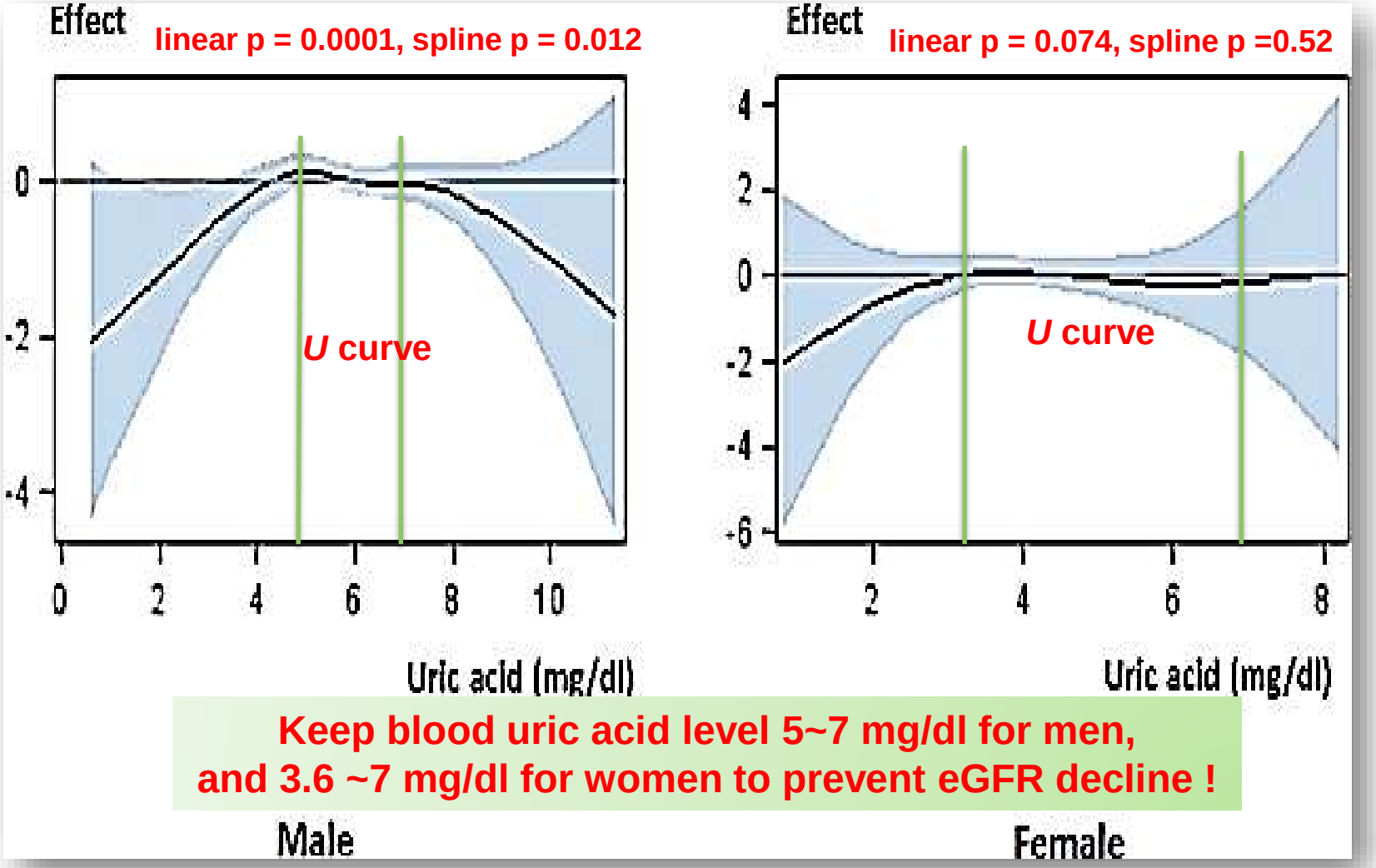
1. Uric Acid Levels, Kidney Function, and Cardiovascular Mortality in US Adults: (NHANES) 1988–1994 and 1999–2002 .
   Am J Kidney Dis. 2014 October; 64(4): 550–557
2. J-shaped mortality relationship for uric acid in CKD.
   Am J Kidney Dis 2006; 48: 761–771

The relationships among hyperuricemia, endothelial dysfunction, and cardiovascular renal diseases: Molecular mechanisms



Paolo Puddu et al. *Journal of Cardiology* 2012, 59(3): 235-242.

Effect of serum uric acid level on eGFR decline

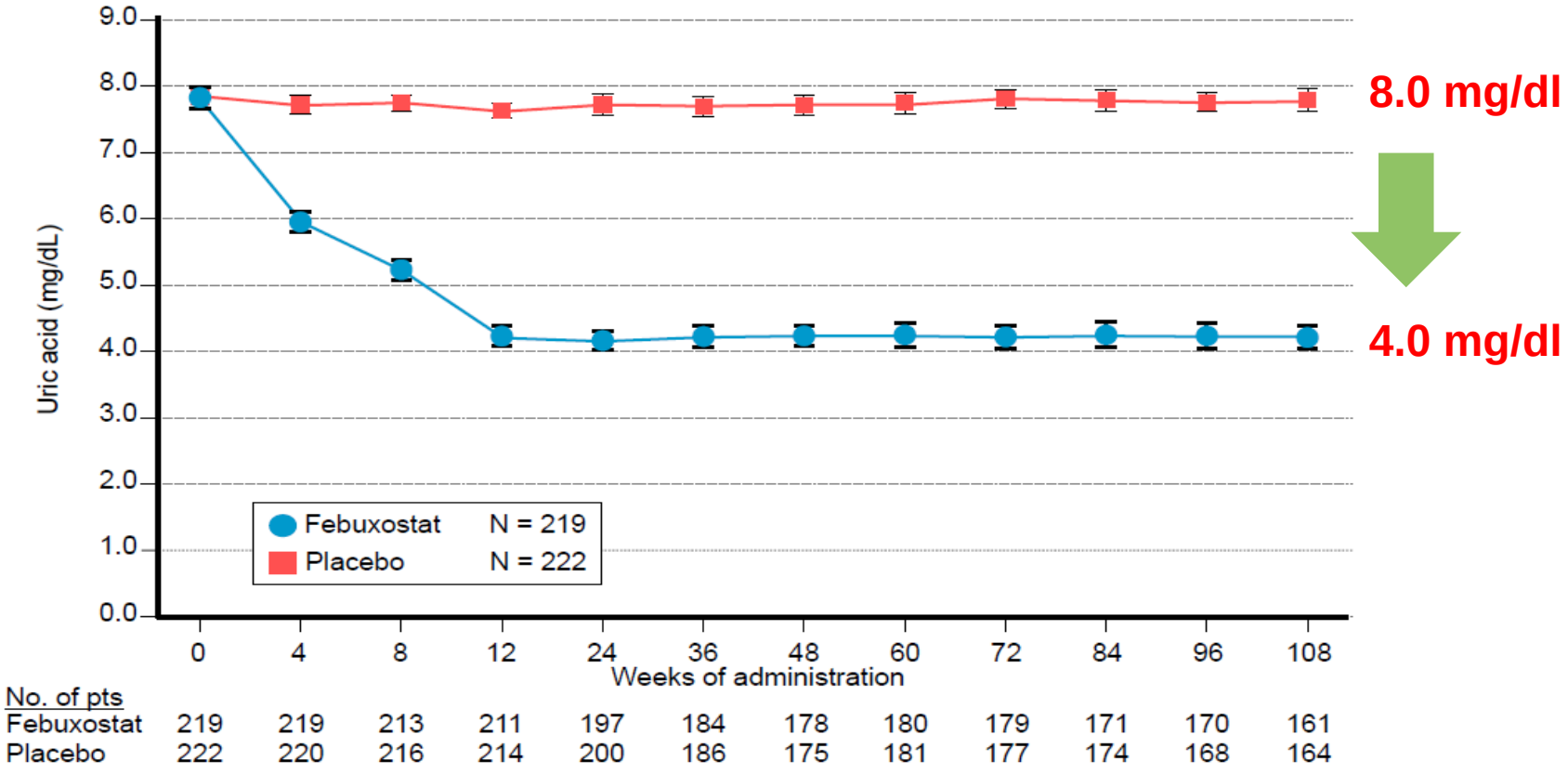


Eiichiro Kanda et al. PLoS One. 2015; 10(2): e0118031

Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial

(the FEATHER Study)

467 patients with stage 3 CKD and asymptomatic hyperuricemia at 55 medical institutions in Japan were included. Participants were randomly assigned in a 1:1 ratio to receive **febuxostat 40 mg** QD or placebo **for 108 weeks**.



Kenjiro Kimura et al. Am J Kidney Dis. 2018; 72(6):798-810.

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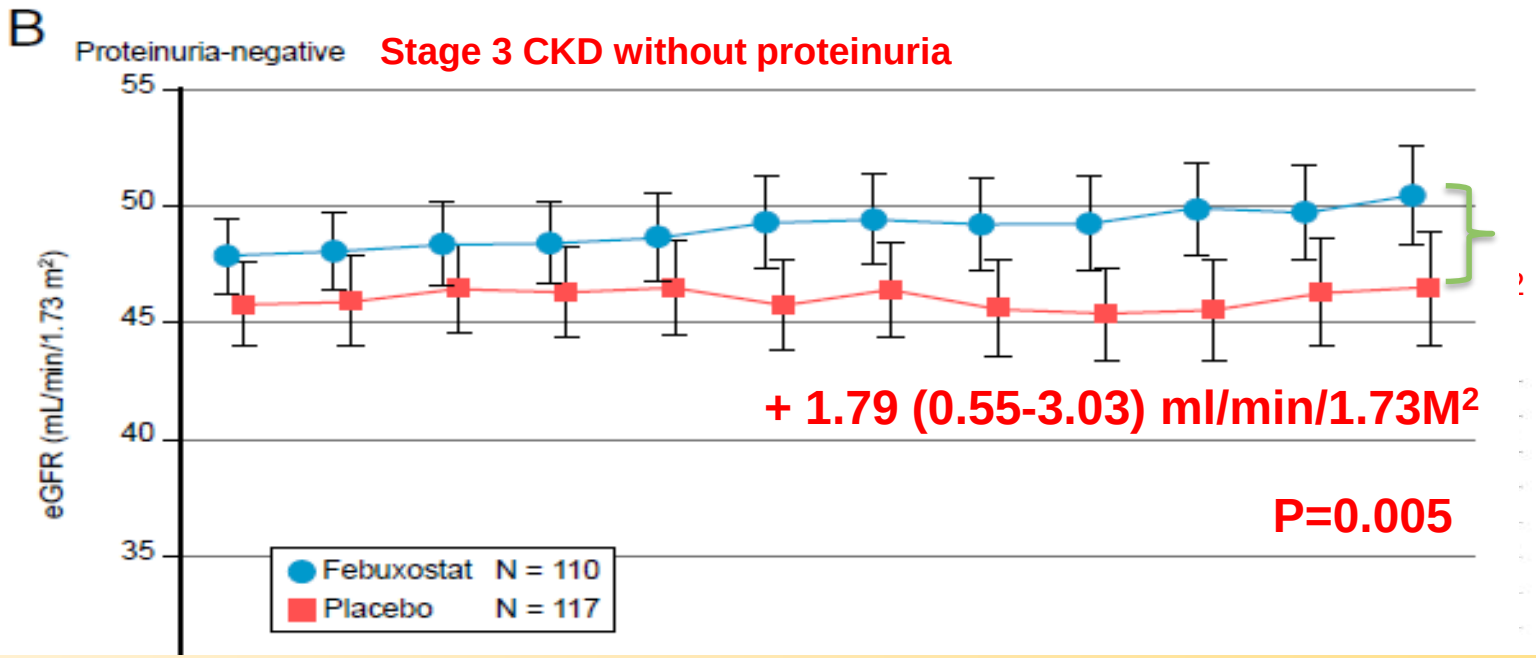
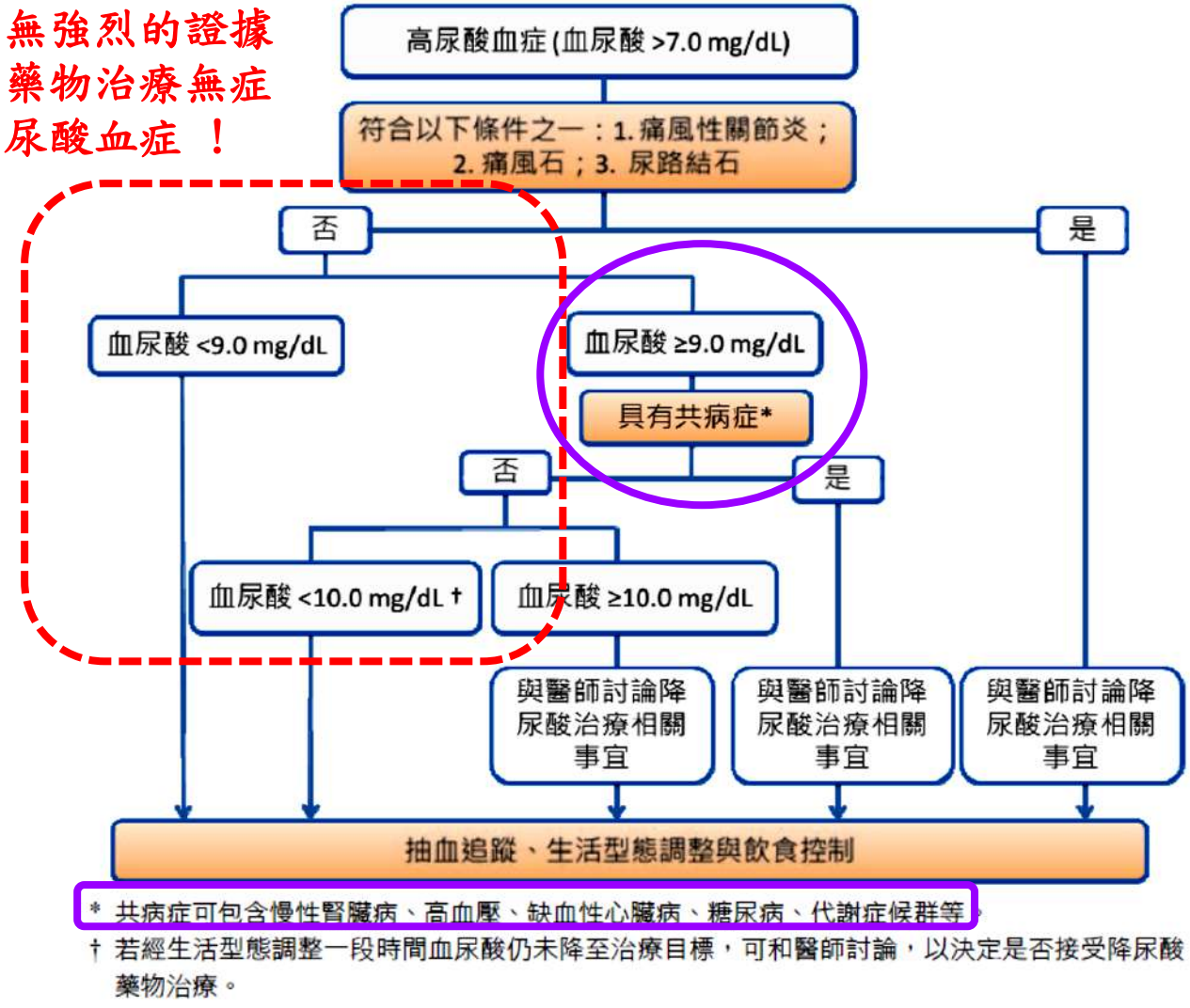


- Compared to placebo, febuxostat did not mitigate the decline in kidney function among patients with stage 3 CKD and asymptomatic hyperuricemia.
- Subgroup analysis demonstrated a significant benefit from febuxostat in patients without proteinuria (P = 0.005) and for whom serum creatinine concentration was lower than the median (P = 0.009).

Kenjiro Kimura et al. Am J Kidney Dis. 2018; 72(6):798-810.

高尿酸血症的全身性影響及最新治療建議

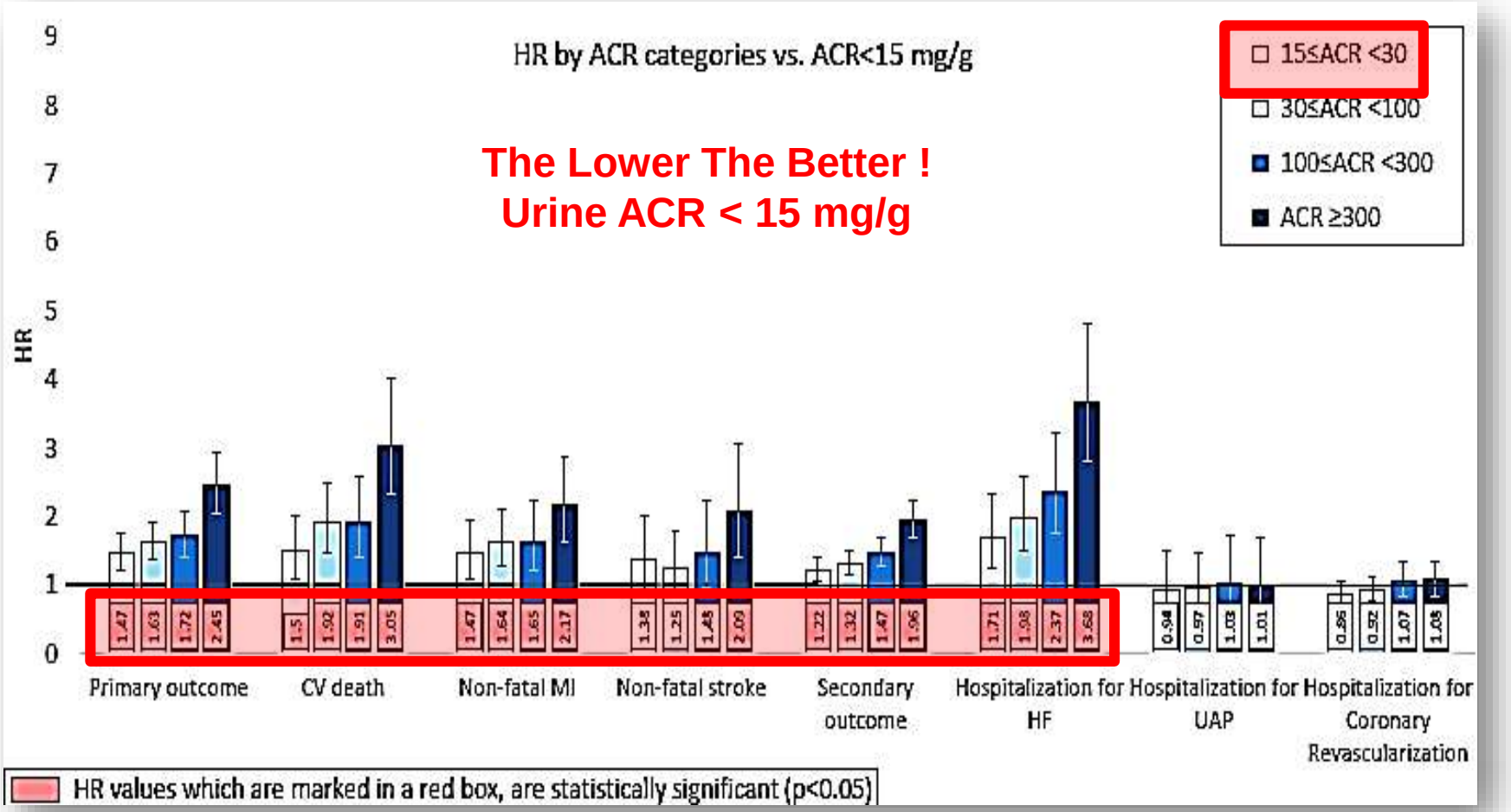
目前尚無強烈的證據
支持用藥物治療無症
狀之高尿酸血症 ！



陳得源. 內科學誌 2018：29：1-7

Proteinuria and Chronic Kidney Disease

Multivariable Cox Proportional Hazard Ratio for the Association of Urine ACR categories with Time to First CV Event: Primary and Secondary Composite Endpoints and their Components



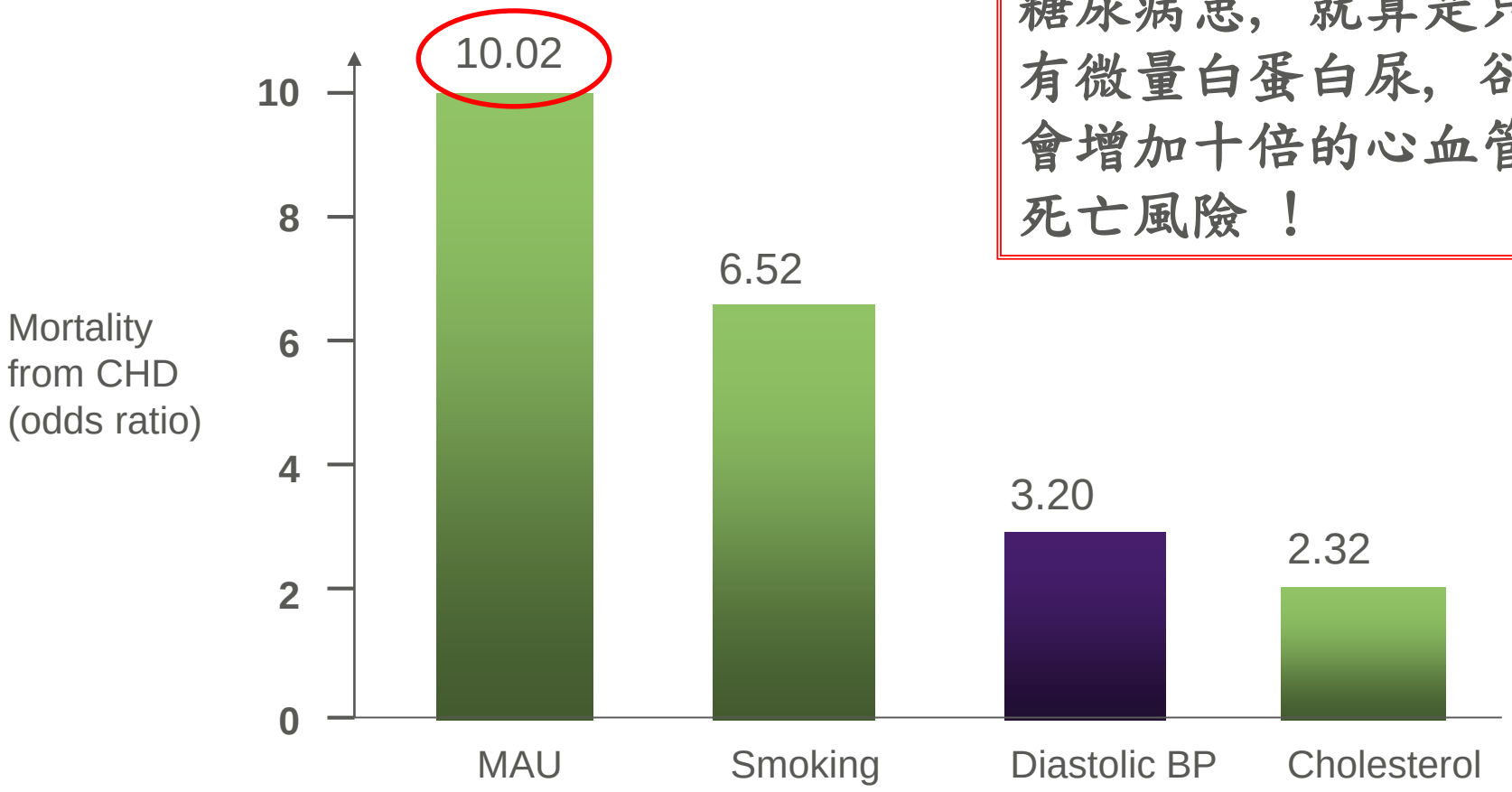
ACR, albumin-creatinine ratio; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; UAP, unstable angina pectoris

Mosenzon O, et al. ADA 2015 Poster 611-P

Microalbumnuria (MAU) predicts CV Risks in Type 2 DM

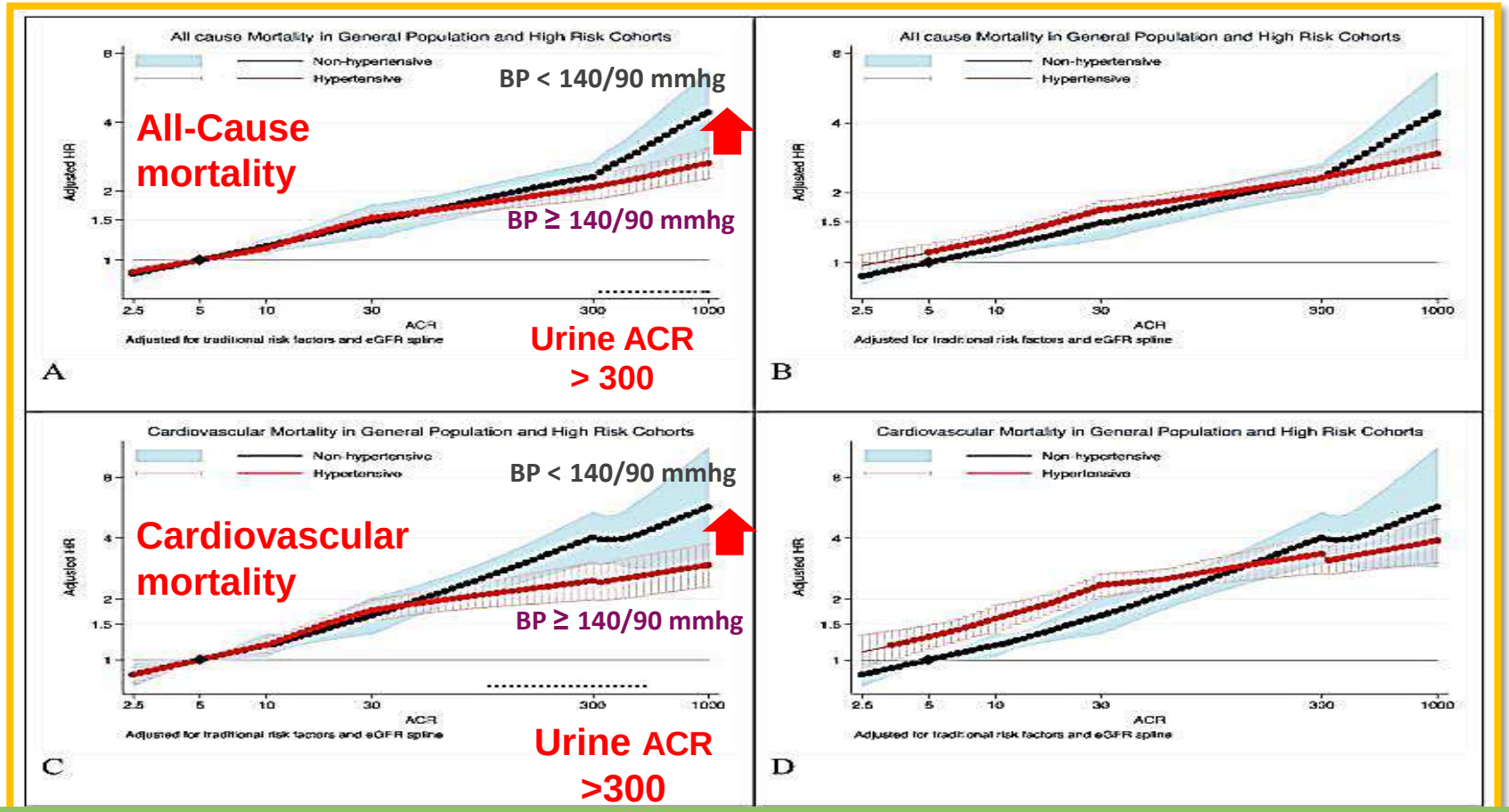
Relative prognostic value of MAU (ACR 30 ~300 mg/g):

糖尿病患，就算是只有微量白蛋白尿，卻會增加十倍的心血管死亡風險 ！



Adapt from Lancet 1997;350(Suppl 1):29–32.

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis (Urine ACR *vs.* Mortality)

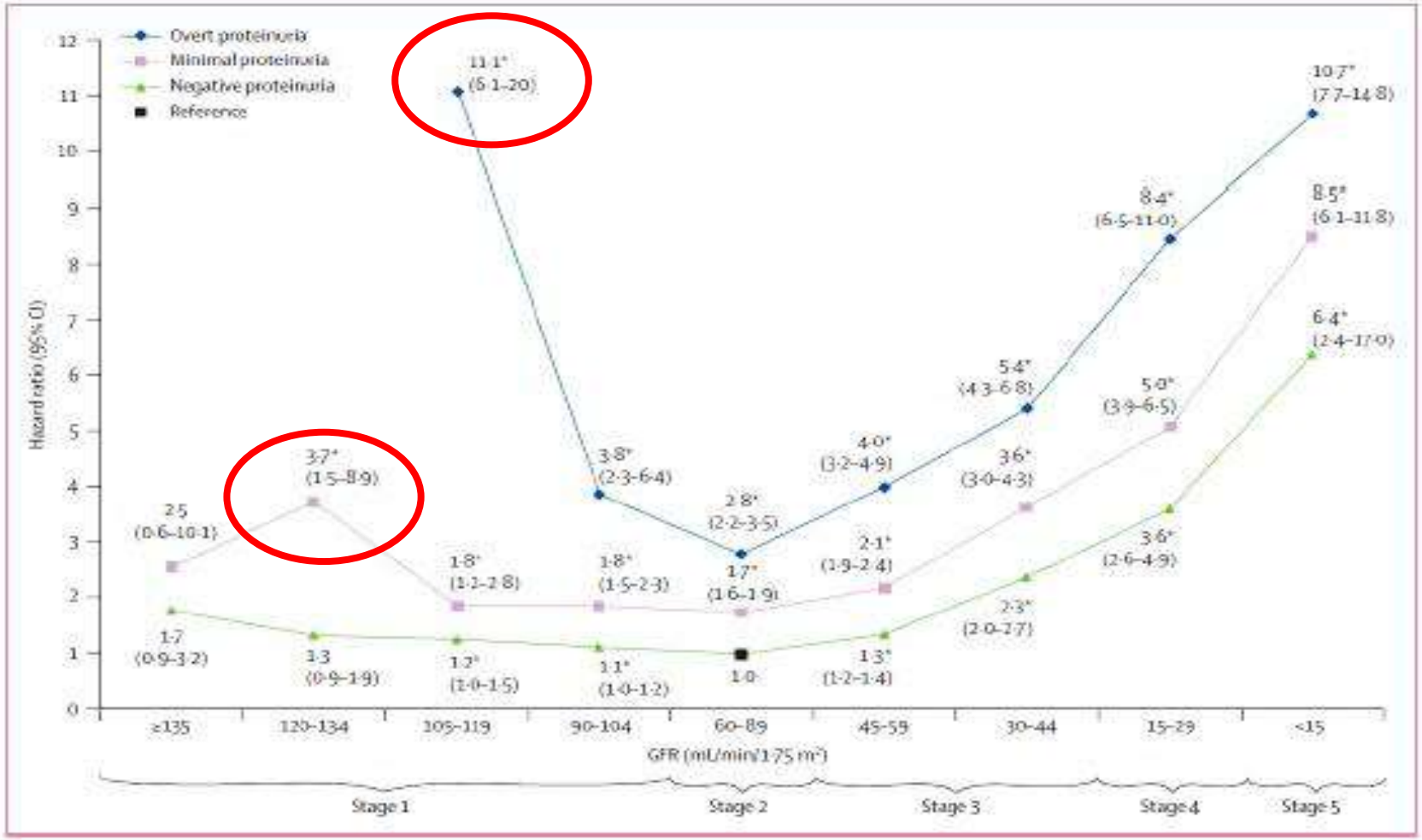


控制血壓也要降低蛋白尿才能有效減少死亡及洗腎的風險！

hypertensives (**black-line**) versus hypertensives (**red-line, BP ≥ 140/90 mmhg**)

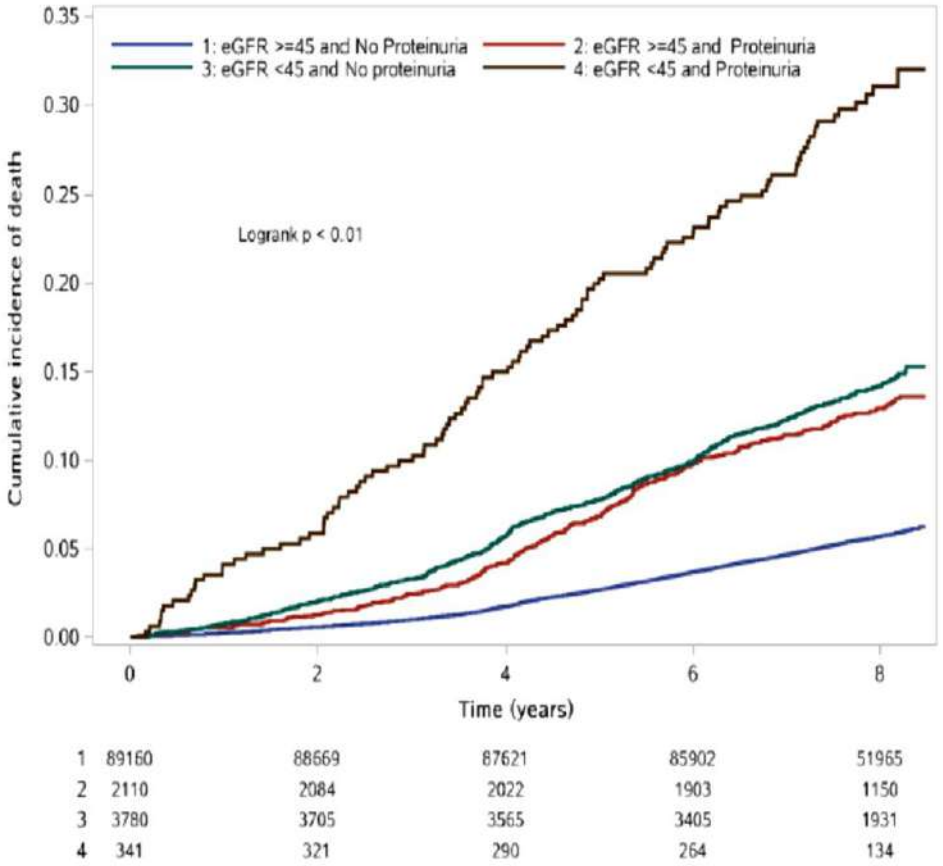
Bakhtawar K. Mahmoodi et al. Lancet. 2012 Nov 10;380(9854):1649-61

Proteinuria and stage of CKD as a predictor in all-cause mortality in Taiwan



Chi Pang Wen et al, Lancet 2008; 371: 2173-82

Association of estimated glomerular filtration rate and proteinuria with all-cause mortality in community-based population in China: A Result from Kailuan Study (n=95391)



eGFR <45 with proteinuria
的死亡率最高

Baseline eGFR (ml/min/1.73 m²)	≥45 HR (95%CI)	<45 HR (95%CI)	P for trend
All-cause mortality			<0.01
No proteinuria	Reference	1.26(1.10–1.44)	
Proteinuria	1.95(1.78–2.14)	2.63(2.14–3.23)	

Jianwei Wu et al. Ssientific Reports | (2018) 8:2157 | DOI:10.1038/s41598-018-20554-3

Double dose ARB demonstrated a more significant reduction in the urinary albumin excretion in T2DM

IRMA2

Urinary albumin excretion

24 % in the irbesartan 150 mg group

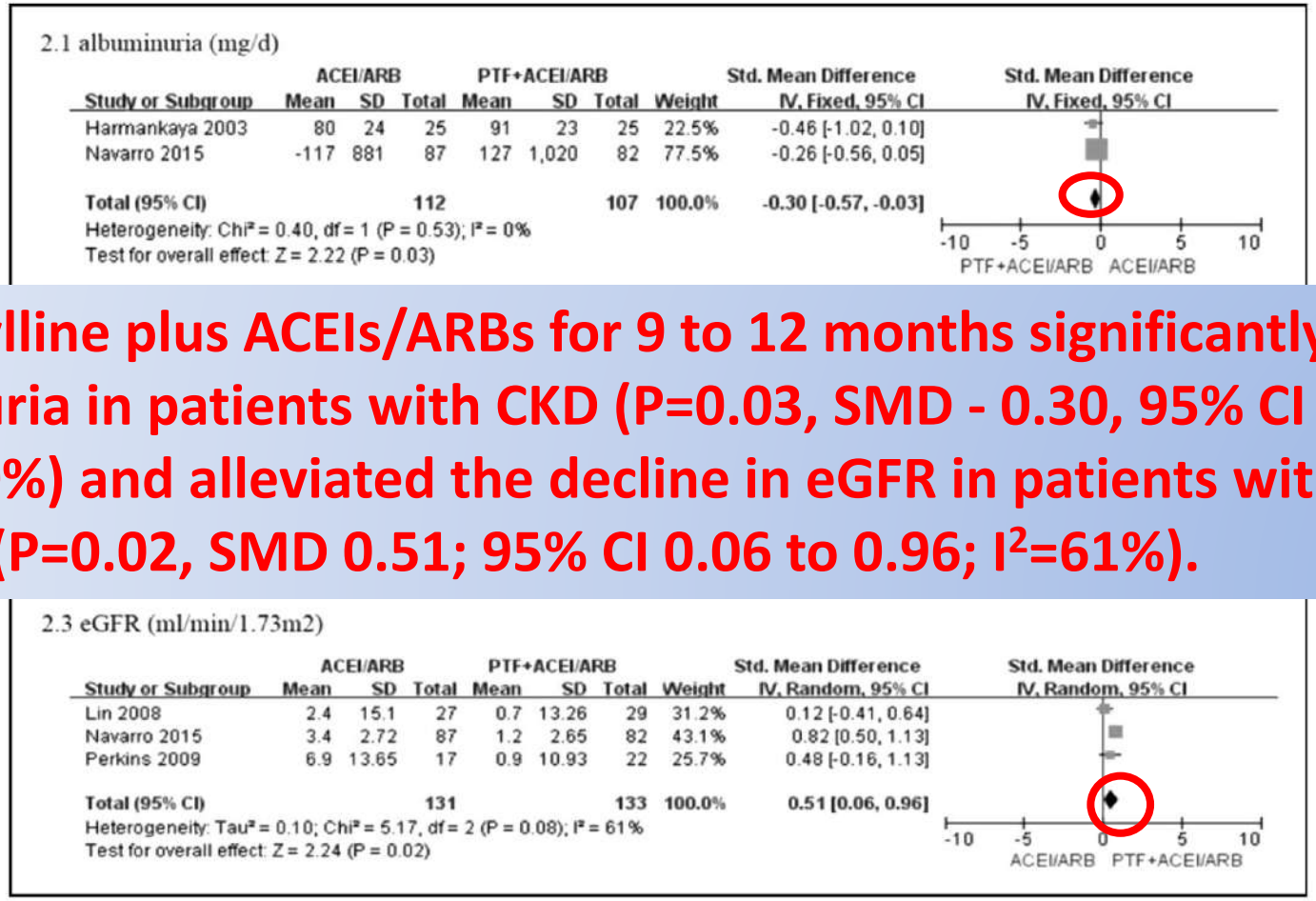
38 % in the irbesartan 300 mg group

vs. 2% in the placebo group

但 AEEI / ARB 用於 eGFR < 30 或 eGFR 急速下降的病患身上,
個人建議劑量應減半再減半, 甚至停藥觀察 eGFR 之變化,
並改以CCB (± statin ± pentoxifylline) 取代做為降尿蛋白藥物！

Parving HH, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Eng J Med 2001;345:870-8.

Pentoxifylline plus ACEIs/ARBs for proteinuria and kidney function in chronic kidney disease: a meta-analysis



Pentoxifylline plus ACEIs/ARBs for 9 to 12 months significantly reduced albuminuria in patients with CKD (P=0.03, SMD - 0.30, 95% CI - 0.57 to 0.03; I^2=0%) and alleviated the decline in eGFR in patients with stages 3–5 CKD (P=0.02, SMD 0.51; 95% CI 0.06 to 0.96; I^2=61%).

Figure 5. Effects of PTF plus ACEI/ARB vs. ACEI/ARB treatment for 9 to 12 months on albuminuria, serum creatinine levels, and eGFR in patients with CKD.

Dong Liu et al. Journal of International Medical Research 2017, Vol. 45(2) 383–398

DM, HTN, Hyperlipidemia, Hyperuricemia and Proteinuria

治療期間沒發生 dialysis, unstable angina, CHF, AMI, Stroke or amputation

1532021338

門診處方簽 XX

領藥號: 920

【重印】

姓 名: 陳先生 年齡: 56歲 男 病歷號: 132

身 份: 健保 卡號: IC 診間: 1208診23號 門診日: 105/05/25

科 別: 腎臟內科 醫師: 徐偉岸 執照: 019662 列印時間: 19:20

診 斷: N189 Chronic kidney disease, unspecified

E1121 Type 2 diabetes mellitus with diabetic nephropathy

I119 Hypertensive heart disease without heart failure

庫序	代碼	名稱	數量	用法	途徑	天	總量	自備註
04 1	THNM5	(KC00899266)＊筆型Humalog Mix 50 100U/ml K	38.00IU	BID	SC	28	8.00vial	SC
04 2	ILANT3	(KC00728266)＊Lantus SoloStar 300U/3ml/via	15.00IU	HS	SC	28	2.00vial	SC
04 3	OSITA1	(BC25043100)＊JanuMET (sitagliptin 50mg/me	1.00粒	BID	PC	28	56.00粒	
04 4	OAMA1	(AB58071100)＊(信東)Glimet tab. (glimepiri	1.00粒	BID	AC	28	56.00粒	
04 5	ODILT	(AC47510100)25mg Carvedilol(CARDIOL)	1.00粒	BID	PC	28	56.00粒	
04 6	OIRBE	(BC22843100)Aprovel 300mg (Irbesartan)	1.00粒	QD	PC	28	28.00粒	
04 7	OBUR	(BC05176100)Burinex(Bumetanide) 1mg/tab	1.00粒	QD	PC	28	28.00粒	
04 8	OCADU1	(BC24392100)Caduet (Amlodipine 5mg/Atorvas	1.00粒	QD	PC	28	28.00粒	
04 9	OEMPA1	(BC26406100)＊Jardiance 10mg (Empagliflo	1.00粒	QD	PC	28	28.00粒	Y
0410	E004	(NAN020632GNR)胰島素注射針頭 6mm	3.00Pc	QD		28	84.00Pc	

HbA1C 9.4%, BP 184/101 mmhg, LDL-C 148.6, UA 9.5, Urine ACR 4688, eGFR 56.8

HTN and DM noted for 10years, BDR, hyperlipidemia, hyperuricemia , smoking (1PPD, 30years),

105/5 -> 108/ 6

HbA1C 6.8%, BP 136/72 mmhg, LDL-C 97, UA 5.4, Urine ACR 561, eGFR 69.5

(Colon microbiota-dysbiosis derived)
Protein-bound uremic toxins and Chronic Kidney Disease

- Oral adsorbents for preventing CVD and CKD progression

Effects of chronic kidney disease on intestinal bacteria metabolism

Effects	Mechanism
1.Reduced intake of dietary fibers	Prescribed potassium restriction leads to reduced intake of fruits and vegetables
2.Prolonged colonic transit time (constipation)	Multifactorial: dialysis modality, lifestyle, inactivity, phosphate binders, dietary restrictions, low fluid intake, primary renal disease, and comorbidities (diabetes, heart failure, malnutrition, cerebrovascular disease)
3.Increased amounts of protein available for proteolytic bacterial species	Protein assimilation is impaired in uremia, with increased amounts of intact proteins reaching the colon
4.Changes of the colonic microbiota	Increased blood ammonia concentrations may change intestinal lumen pH; drug therapies (antibiotics, phosphate binders, antimetabolites etc.) with local effect in the gut lumen
5.Increased permeability of the intestinal barrier	Uremia; hypervolemia and intestinal ischemia caused by aggressive ultrafiltration volumes or intradialytic hypotension

Sabatino A et al. Nephrol Dial Transplant, 2015, 30:924–933.

Altered microbiome in chronic kidney disease: systemic effects of gut-derived uremic toxins

Gut bacteria produce more Uremic toxins and ammonia.

Reflux of Uremic toxins to blood stream.

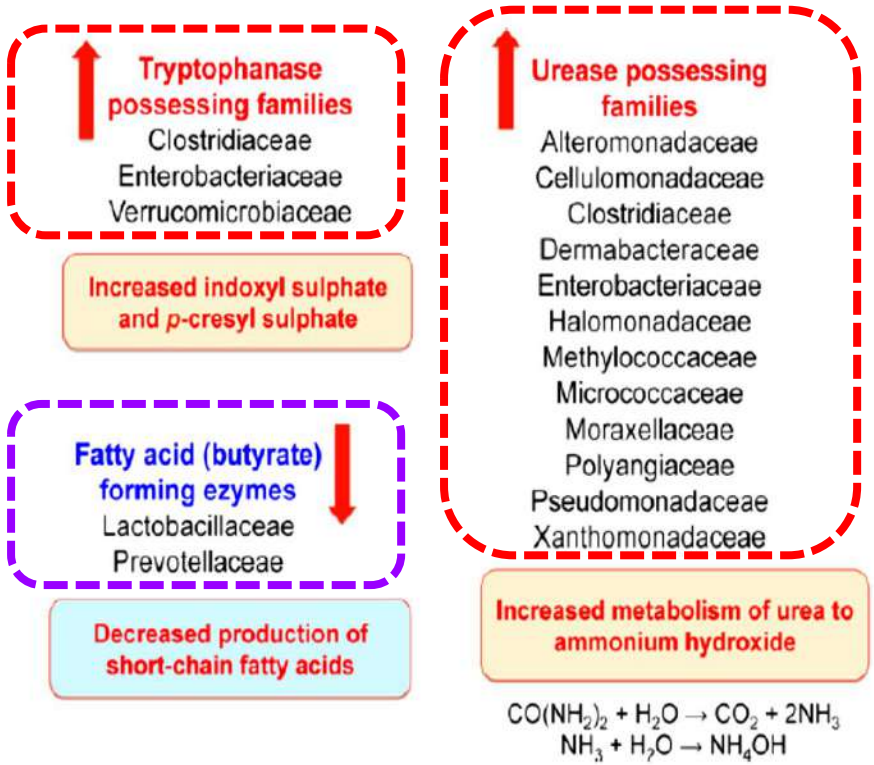


Figure 2. The gut microbiome in CKD shows expansion of bacterial families that express indole and *p*-cresyl enzymes which generate toxins from tryptophan

There is also expansion of microbial families that express urease which contributes to gut wall inflammation as follows: urea diffuses from the blood into the gut lumen and is metabolized by bacterial urease to ammonia [$CO(NH_2)_2 + H_2O \rightarrow CO_2 + 2NH_3$]; ammonia is hydrolyzed into caustic ammonium hydroxide [$NH_3 + H_2O \rightarrow NH_4OH$] which causes enterocyte damage. Finally, there is a decrease in bacterial families that produce short-chain fatty acids which are an essential nutrient source for the host enterocytes.

Wei Ling Lau et al. Clinical Science 2018,132; 509–522.

Altered microbiome in chronic kidney disease: systemic effects of gut-derived uremic toxins

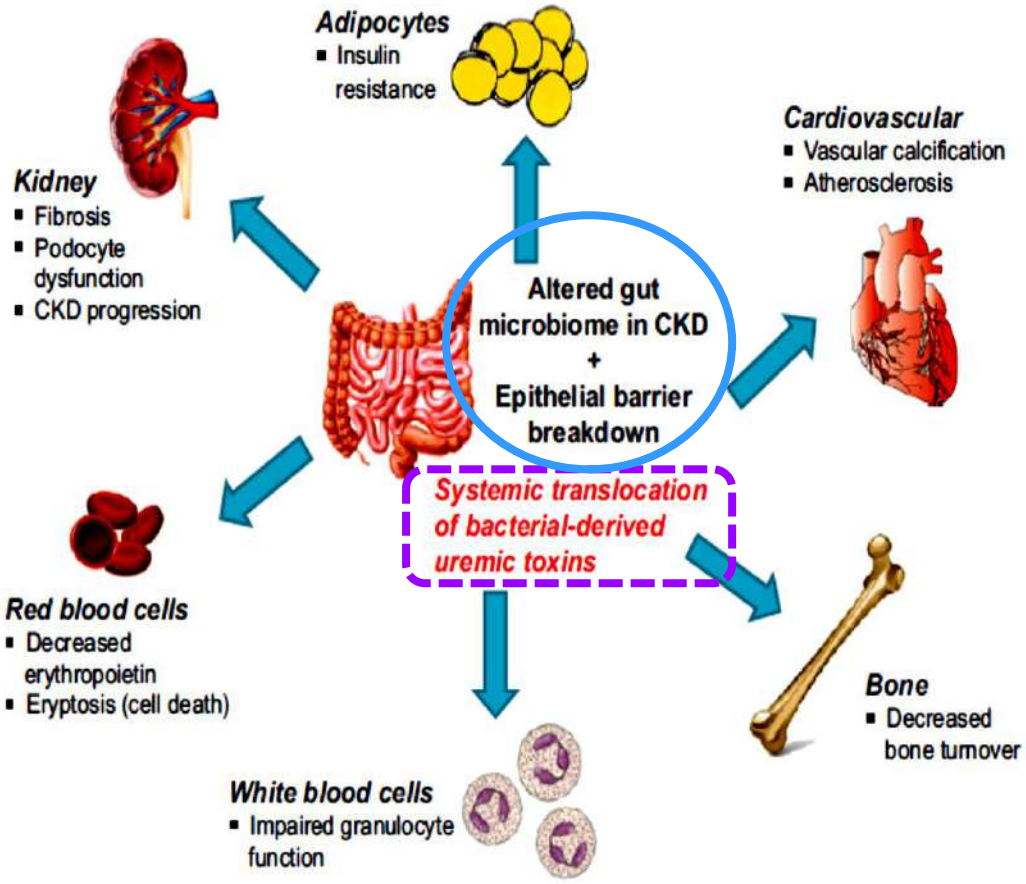
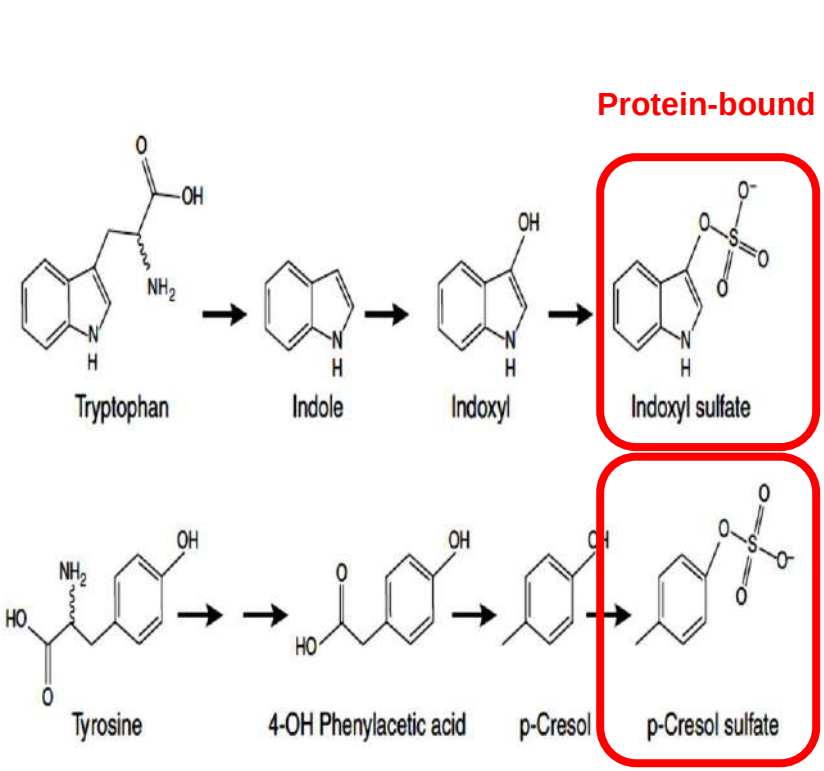


Figure 1. Microbiome alterations and the leaky gut epithelial barrier in CKD results in systemic translocation of bacterial-derived uremic toxins such as indoxyl sulphate and *p*-cresyl sulphate

These toxins induce oxidative stress and damage in multiple organ systems.

Wei Ling Lau et al. Clinical Science 2018,132; 509–522.

Uremic solutes from colon microbes in CKD



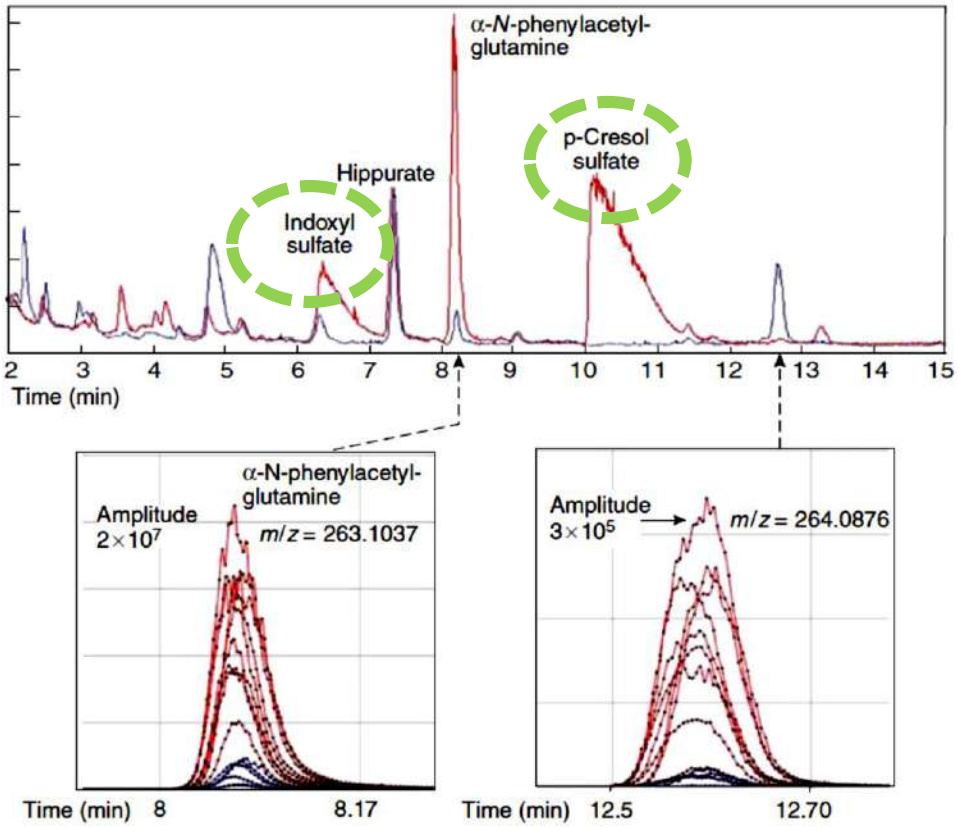
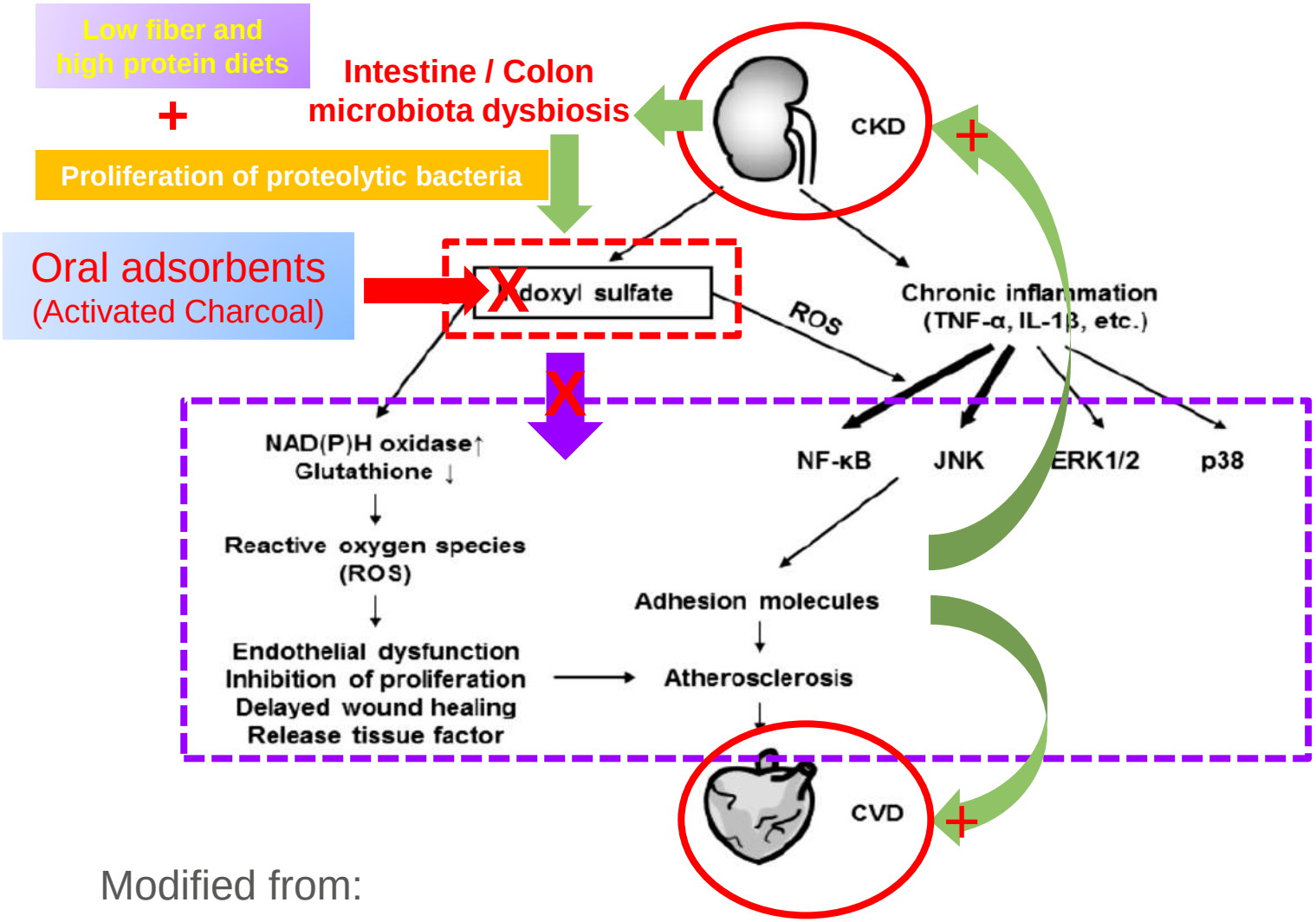


Fig. The identification of colon-derived solutes by mass spectrometry

Timothy W. Meyer and Thomas H. Kidney International 2012; 81, 949–954.

Protein-Bound Uremic Toxins: New Culprits of Cardiovascular Events in Chronic Kidney Disease Patients



Modified from:

Shunsuke Ito and Masayuki Yoshida. Kidney International 2012; 81, 949–954.

Impact of Altered Intestinal Microbiota on Chronic Kidney Disease Progression

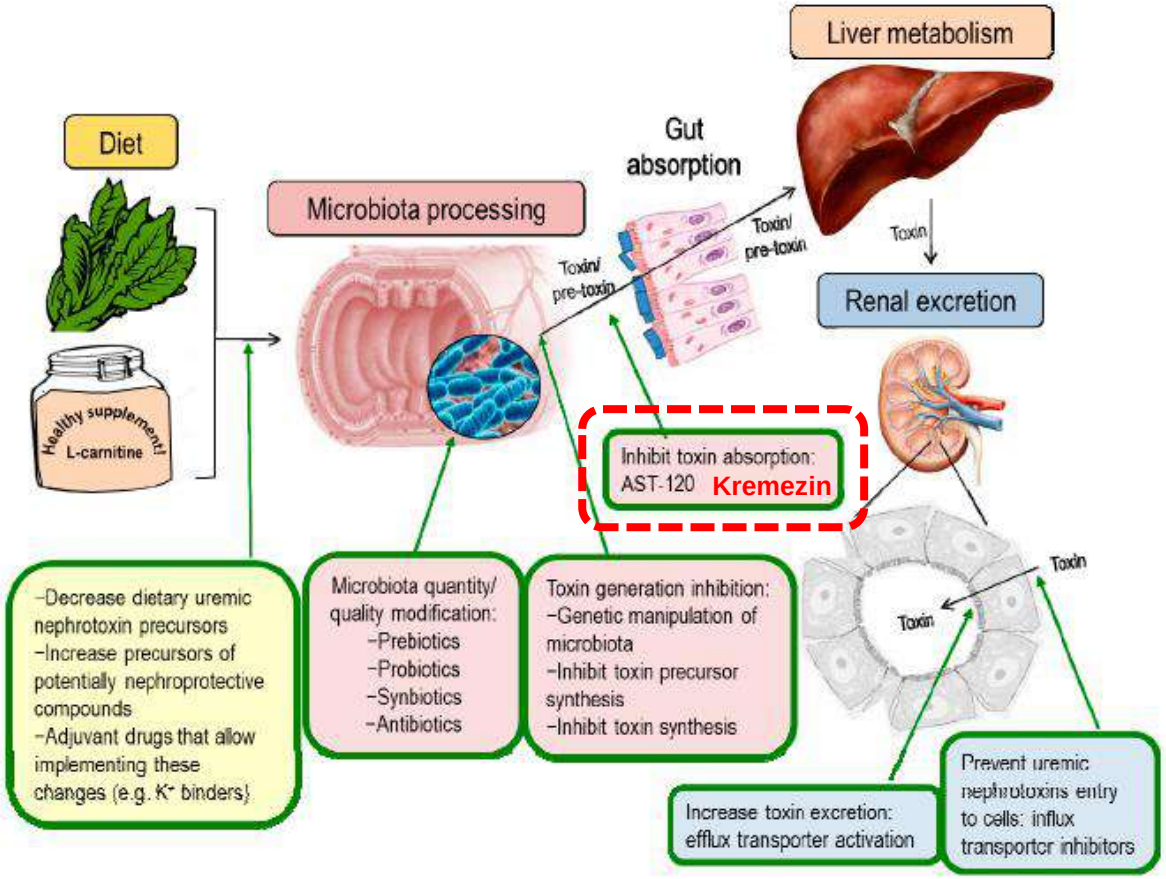
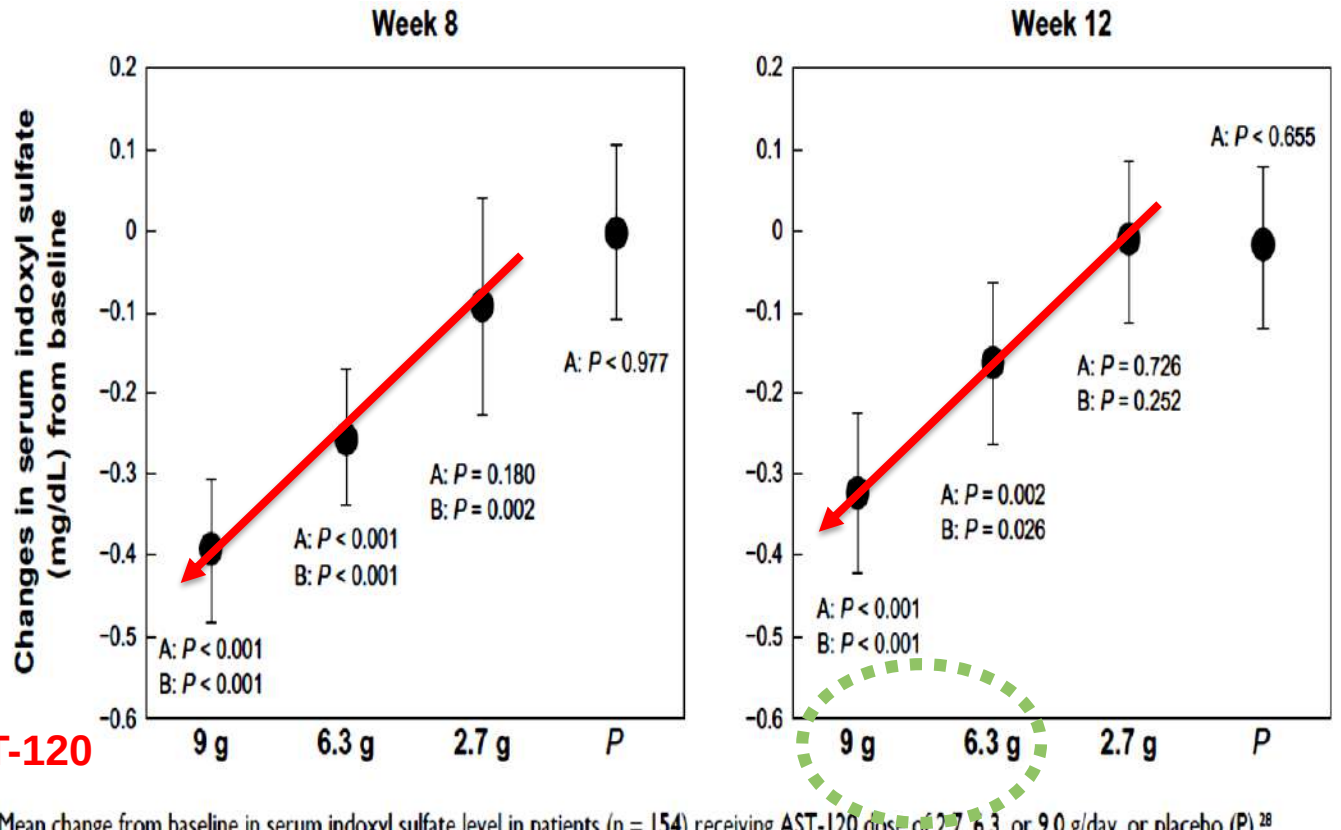


Figure 2. Potential therapeutic approaches on the gut microbiota-CKD progression axis. Only one of these approaches is used routinely in the clinic in some countries (AST-120). The rest are theoretical or have been tested only in preclinical cell culture or animal models.

Esmeralda Castillo-Rodriguez et al. Toxins 2018, 10, 300; doi:10.3390/toxins10070300

AST-120 (Kremezin) for the management of progression of chronic kidney disease

Indoxyl sulfate



Dose of AST-120

Figure 3 Mean change from baseline in serum indoxyl sulfate level in patients (n = 154) receiving AST-120 dose of 2.7, 6.3, or 9.0 g/day, or placebo (P).[28]
Reprinted with permission from Schulman G, Agarwal R, Acharya M, Berl T, Blumenthal S, Kopyt N. A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of AST-120 (Kremezin) in patients with moderate to severe CKD. *Am J Kidney Dis.* 2006;47(4):565–577.[28] © 2006 Elsevier and the National Kidney Foundation.
Notes: A, versus baseline; B, versus placebo.

Gerald Schulman et al. International Journal of Nephrology and Renovascular Disease 2014:7 49–56

Effect of a Carbonaceous Oral Adsorbent (AST-120) on the Progression of CKD: A Multicenter, Randomized, Controlled Trial

Total 75 medical facilities, 460 patients with CKD with serum creatinine (sCr) concentrations less than 5.0 mg/dL (not undergoing dialysis) were randomly assigned to either a low-protein diet and antihypertensive medication in the control group or that treatment combined with **AST-120 (6 g/d).** Composite primary end point: doubling of sCr level, increase in sCr level to 6.0 mg/dL or more, need for dialysis or transplantation, or death.

primary end point

Kremezin 6 g/day

Secondary end point

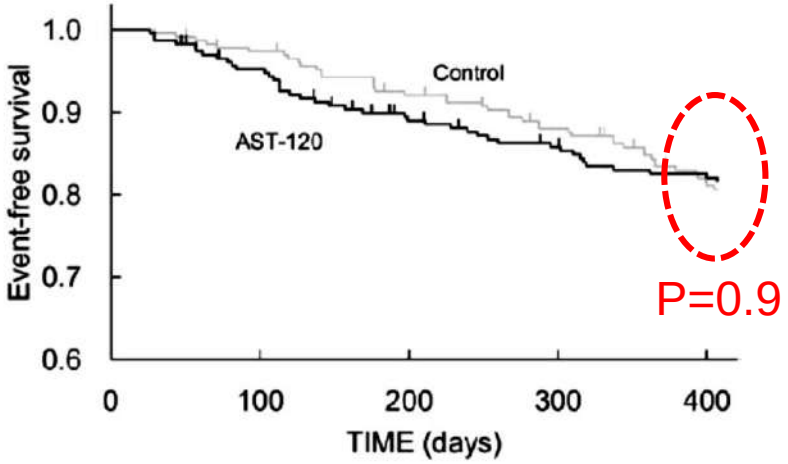


Figure 2. Length of survival before reaching the primary end point, by treatment group. Short vertical tick marks indicate censored data. The difference between groups was not statistically significant ($P = 0.9$, log-rank test).

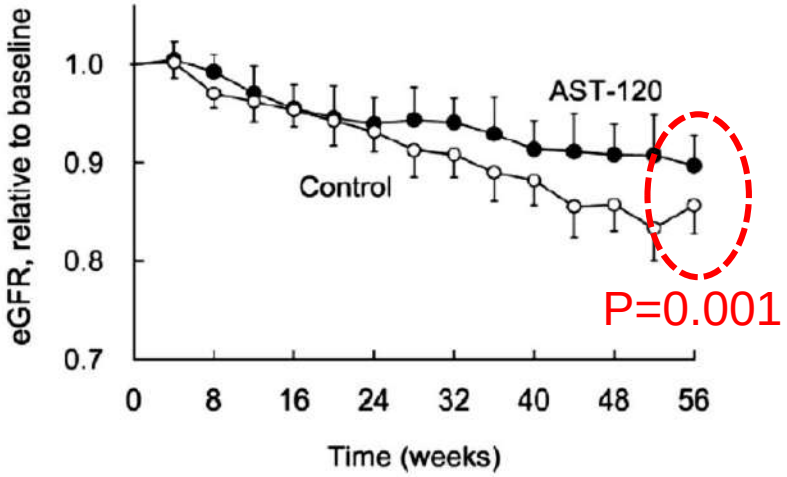


Figure 3. Estimated glomerular filtration rate (eGFR; estimated as described in Matsuo et al[18]) over time, by treatment group. Vertical lines indicate 95% confidence intervals.

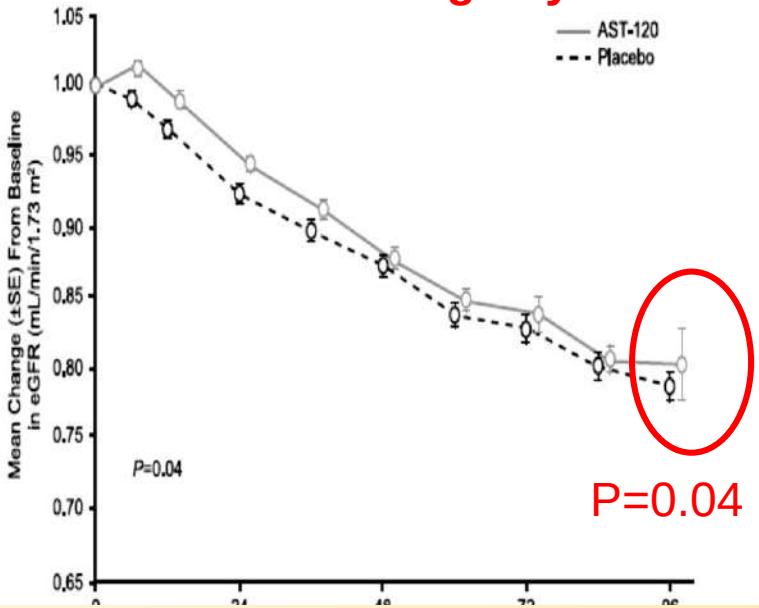
Estimated eGFR decreased more in the control group than in the AST-120 group (- 0.15 versus - 0.12 mL/min/yr; P=0.001).

Tadao Akizawa et al. Am J Kidney Dis 2009; 54:459-467.

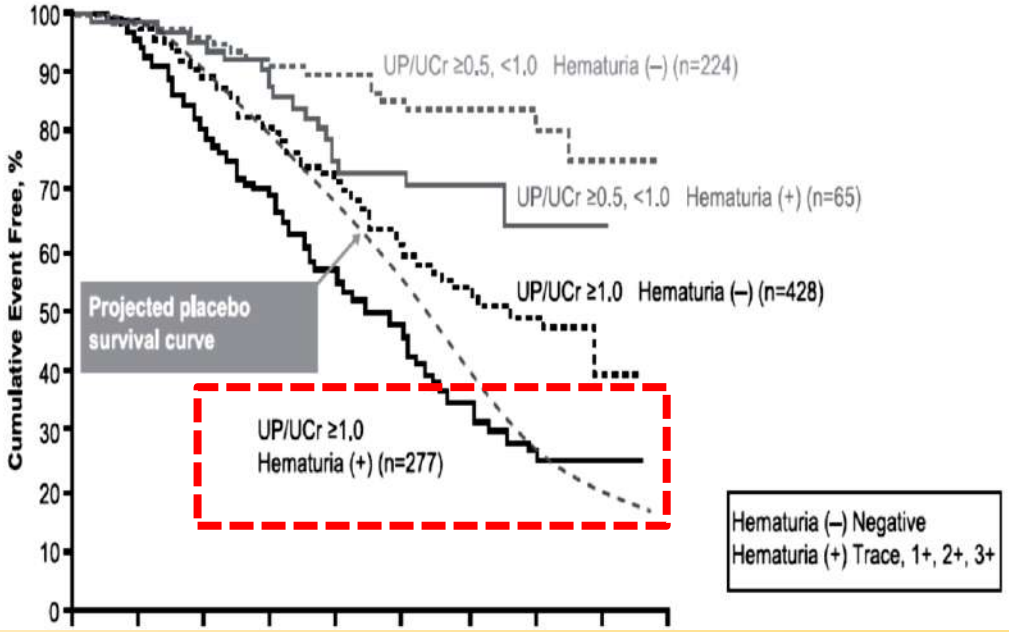
Randomized Placebo-Controlled EPPIC Trials of AST-120 in CKD

The multinational, randomized, double-blind, placebo-controlled Evaluating Prevention of Progression in CKD (EPPIC)-1 and EPPIC-2 trials evaluated the effects of AST-120 on the progression of CKD when added to standard therapy. We randomly assigned 2035 adults with moderate to severe disease (serum creatinine at screening, 2.0–5.0 mg/dl for men and 1.5–5.0mg/dl for women) to receive either placebo or **AST-120 (9 g/d).** The primary end point was a composite of dialysis initiation, kidney transplantation, and serum creatinine doubling.

Kremezin 9 g/day



P=0.04

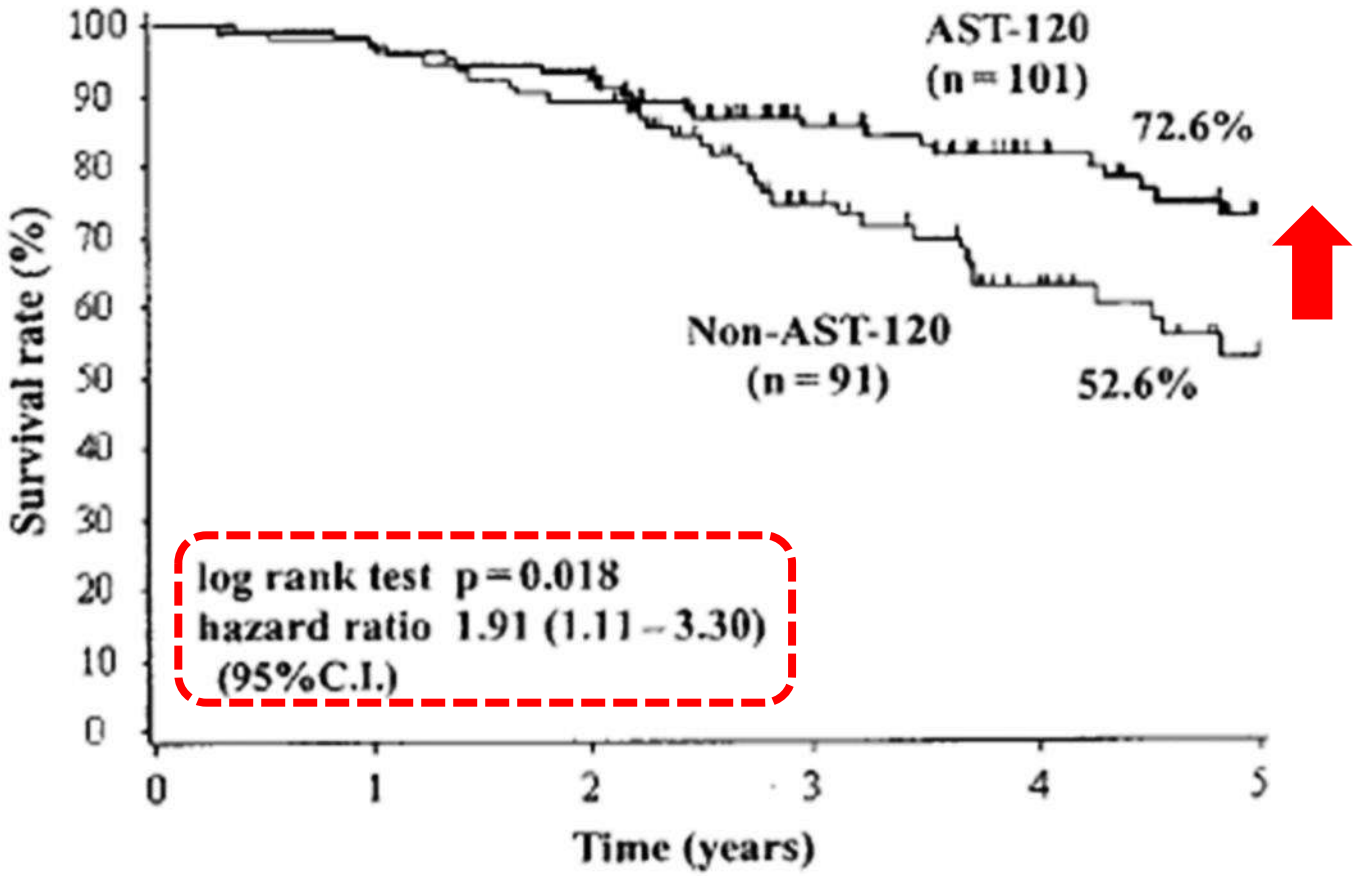


The time to primary end point was similar between the AST-120 and the placebo groups in both trials (EPPIC-1: hazard ratio, 1.03; 95% confidence interval, 0.84 to 1.27; P=0.78) (EPPIC-2: hazard ratio, 0.91; 95% confidence interval, 0.74 to 1.12; P=0.37); a pooled analysis of both trials showeds imilar results.

Gerald Schulman et al. J Am Soc Nephrol 2015; 26: 1732–1746.

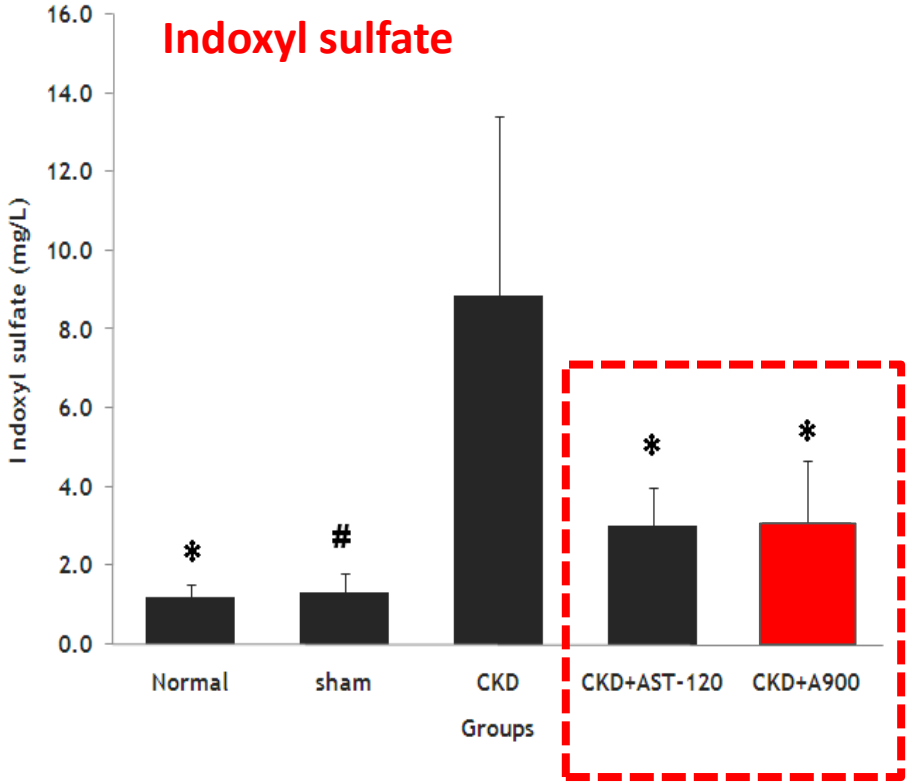
AST-120 treatment in pre-dialysis period affects the prognosis in patients on hemodialysis.

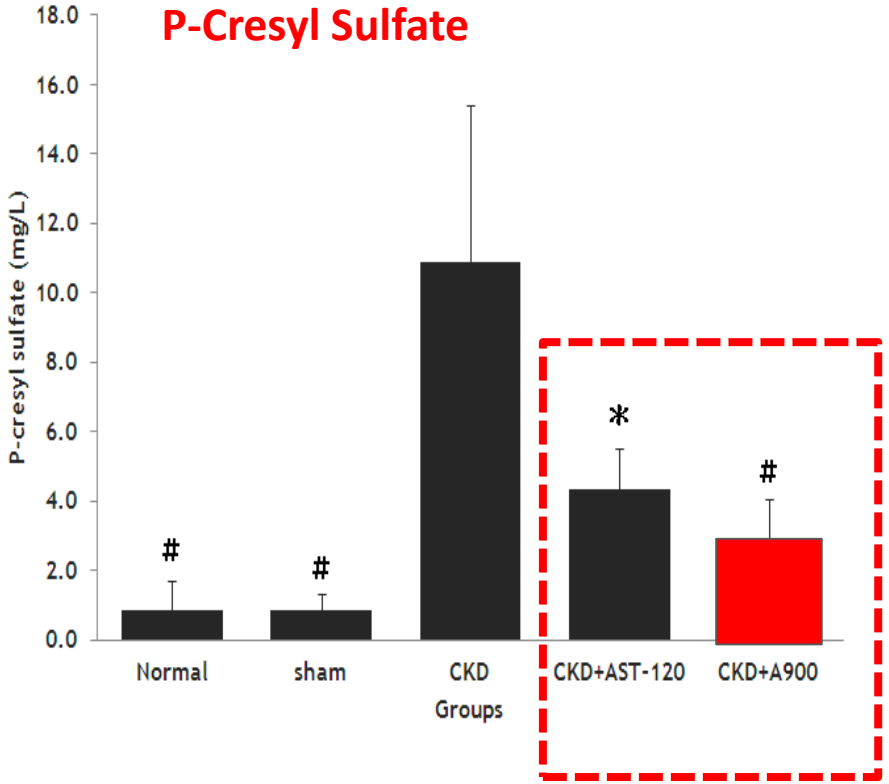
One hundred and ninety-two CKD patients on dialysis were studied. The survival and causes of death after the initiation of dialysis were compared between patients who were administrated AST-120 (AST-120 group, n = 101) and those not administrated AST-120 (non-AST-120 group, n = 91) prior to the initiation of dialysis.



Ueda H et al. Ren Fail. 2008;30(9):856-60.

Comparable adsorbent effects between A900 (CharXgen) and AST-120 (Kremezin)



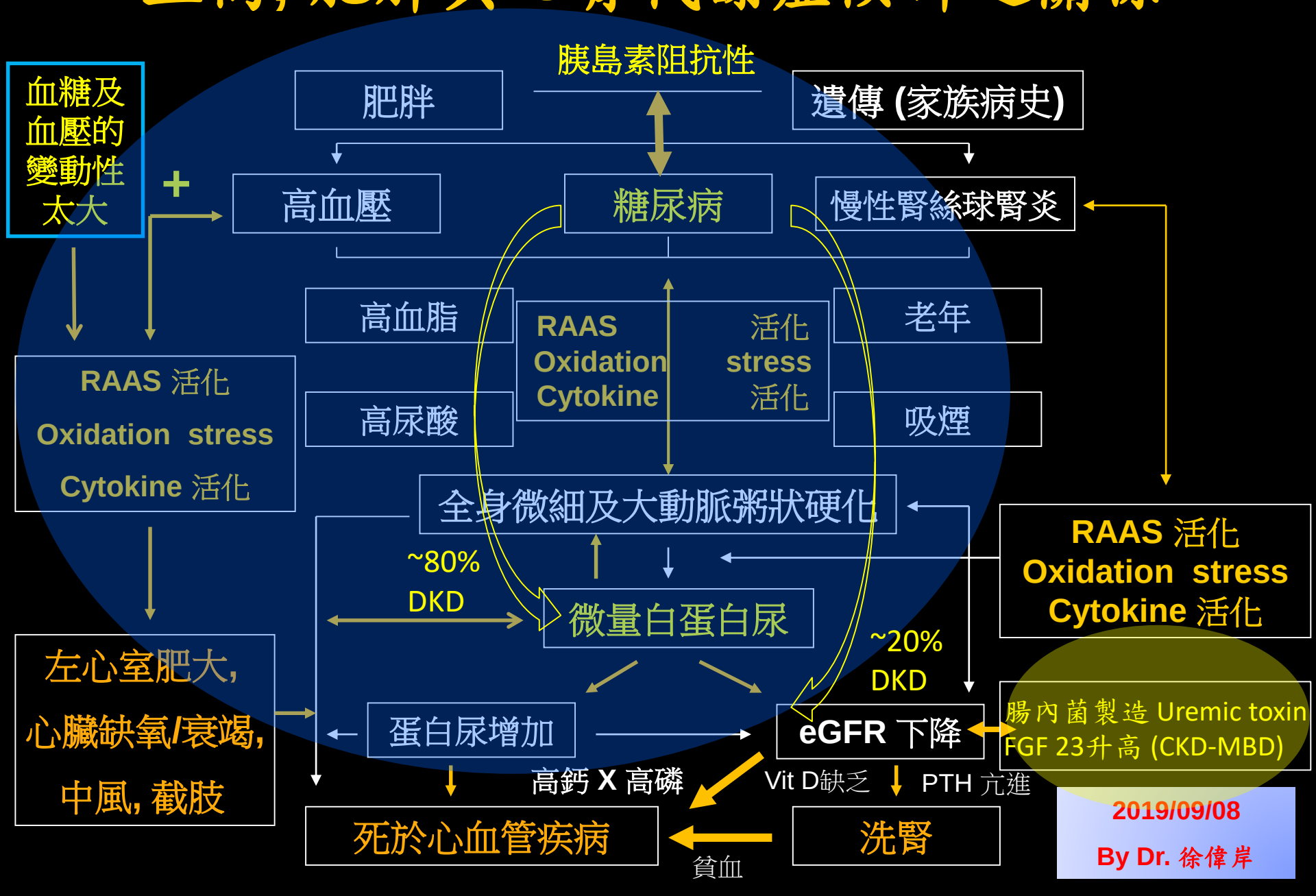


#P<0.01; *P<0.05, compared with CKD group

Unpublished data, for reference only

總結

五高，肥胖與心腎代謝症候群之關係



謝謝聆聽 ！

郡大山之秋景
2018/10/21 徐偉岸攝影